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 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 (ctDNA) or circulating tumor cell testing (also known as a liquid biopsy) is proposed as a non-invasive alternative.
OBJECTIVE

The objective of this evidence review is to determine whether genetic testing for KRAS, NRAS, and BRAF improves the net health outcome in individuals with metastatic colorectal cancer by predicting treatment response.

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 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-epidermal growth factor receptor 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, NRAS, 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 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

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 evidence 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.

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Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td></td>
<td>variant</td>
<td></td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
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</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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

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).

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FDA 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 1):

Table 1. Companion Diagnostic Tests for the Selection of Cetuximab and Panitumumab for Metastatic Colorectal Cancer

<table>
<thead>
<tr>
<th>Diagnostic Name</th>
<th>PMA/510(k)/HDE</th>
<th>Description</th>
<th>Approval Date</th>
<th>Diagnostic Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>FoundationOne CDx</td>
<td>P170019</td>
<td>Next Generation Sequencing Oncology Panel, Somatic Or Germline Variant Detection System</td>
<td>11/30/2017</td>
<td>Foundation Medicine, Inc.</td>
</tr>
<tr>
<td>Praxis Extended RAS Panel</td>
<td>P160038</td>
<td>Next Generation Sequencing Oncology Panel, Somatic Or Germline Variant Detection System</td>
<td>06/29/2017</td>
<td>Illumina, Inc.</td>
</tr>
<tr>
<td>cobas KRAS Mutation Test</td>
<td>P140023</td>
<td>Somatic Gene Mutation Detection System</td>
<td></td>
<td>Roche Molecular Systems, Inc</td>
</tr>
<tr>
<td>therascreen KRAS RGQ PCR Kit</td>
<td>P110030</td>
<td>Somatic Gene Mutation Detection System</td>
<td>5/23/2014</td>
<td>Qiagen Manchester, Ltd.</td>
</tr>
<tr>
<td></td>
<td>P110027</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

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Liquid Biopsy

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

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. The relevant outcomes are 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 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. 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 RCTs. 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 ctDNA or CTC 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 ctDNA and CTC, 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% CI 87% to 100%) and specificity ranged from 83% (95% CI 71% to 92%) to 94% (82% to 98%). FoundationOne Liquid has been compared to tissue biopsy with the FoundationACT 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

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SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (v.2.2018) guidelines on the treatment of colon cancer recommend that tumor tissue should be genotyped for RAS (KRAS and NRAS) and BRAF variants, individually or as part of a next-generation sequencing panel, for all patients with metastatic colon cancer (v.2.2019). Testing should be performed on archived specimens of the primary tumor or 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. Individuals with KRAS variant in exons 2, 3, or 4, or with NRAS variant in exons 2, 3, or 4, are not eligible for treatment with cetuximab or panitumumab. The guidelines also state that the presence of the BRAF V600E variant makes a response to panitumumab and cetuximab highly unlikely. However, the concurrent administration of a BRAF inhibitor may make a response to these treatments more likely.

The guidelines for colon cancer (v.2.2019) reference a paper on circulating tumor DNA in the discussion of adjuvant chemotherapy in stage II disease with the statement "Research into additional possible predictive markers may allow for more informed decision-making in the future." 

American College of Medical Genetics and Genomics

An evidence review published by the American College of Medical Genetics and Genomics (2013) 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. That same review further found no guidelines on NRAS testing from any other U.S. group.

The American Society of Clinical Oncology along with American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology (2017) published guidelines on molecular biomarkers for the evaluation of colorectal cancer. Table 2 summarizes the relevant guidelines.

Table 2. Summary of Recommendations

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Type</th>
<th>SOE</th>
<th>QOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>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 (&quot;expanded&quot; or &quot;extended&quot; RAS)</td>
<td>Recommendation</td>
<td>Convincing/adequate, benefits outweigh harms</td>
<td>High/intermediate</td>
</tr>
</tbody>
</table>

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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

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Adequate/inadequate, balance of benefits and harms</th>
<th>Intermediate/low</th>
</tr>
</thead>
</table>

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 sporadic pathogenesis. The absence of BRAF mutation does not exclude risk of Lynch syndrome

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Adequate/inadequate, balance of benefits and harms</th>
<th>Intermediate/low</th>
</tr>
</thead>
</table>

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

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Adequate/inadequate, balance of benefits and harms</th>
<th>Intermediate/low</th>
</tr>
</thead>
</table>

There is insufficient evidence to recommend BRAF c.1799 p.V600 mutational status as a predictive molecular biomarker for response to anti-EGFR inhibitors

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Insufficient, benefits/harms balance unknown</th>
<th>Insufficient</th>
</tr>
</thead>
</table>

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

The American Society of Clinical Oncology (2015) updated its provisional clinical opinion on extended RAS variant testing in metastatic colorectal cancer to predict response to anti-EGFR monoclonal antibody therapy. 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 were small, and there was inadequate evidence to provide a definitive opinion on the lack of benefit for the use of anti-epidermal growth factor receptor 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 suggested the same lack of benefit with anti-epidermal growth factor receptor therapy as seen with the more common variants in exon 2 of KRAS.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

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Medicare National Coverage

A March 2018 decision memo from the Centers for Medicare & Medicaid Services addressed next-generation sequencing for Medicare beneficiaries with advanced cancer. The memo states:

The Centers for Medicare & Medicaid Services has determined that Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally when performed in a CLIA-certified laboratory, when ordered by a treating physician and when all of the following requirements are met:

1. Patient has:
   a. either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and
   b. either not been previously tested using the same NGS test for the same primary diagnosis of cancer or repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physician; and
   c. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

2. The diagnostic laboratory test using NGS must have:
   a. Food and Drug Administration approval or clearance as a companion in vitro diagnostic; and
   b. a Food and Drug Administration approved or cleared indication for use in that patient's cancer; and
   c. results provided to the treating physician for management of the patient using a report template to specify treatment options.

Regarding liquid biopsies, the memo states, "The NCD does not limit coverage to how to prepare a sample for performing a diagnostic laboratory test using NGS. Commenters submitted published articles on liquid biopsies (also referred to as circulating tumor DNA (ctDNA) or plasma cell-free DNA (cfDNA) tests). We reviewed and included in the evidence and analysis of four studies on liquid biopsies. At this time, liquid-based multi-gene sequencing panel tests are left to contractor discretion if certain patient criteria are met."

REFERENCES


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


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**POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 2012</td>
<td>New policy</td>
<td>Policy updated with literature review. No references added. Policy statements unchanged except for minor wording change in statement on KRAS testing.</td>
</tr>
<tr>
<td>March 2013</td>
<td>Replace policy</td>
<td>Policy updated with literature review, Reference 14 added, policy statements unchanged.</td>
</tr>
<tr>
<td>March 2014</td>
<td>Replace policy</td>
<td>Policy updated with literature review. No references added. Policy statements unchanged except for minor wording change in statement on KRAS testing.</td>
</tr>
<tr>
<td>March 2015</td>
<td>Replace policy</td>
<td>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.</td>
</tr>
<tr>
<td>March 2018</td>
<td>Replace policy</td>
<td>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”.</td>
</tr>
<tr>
<td>September 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through May 10, 2018; no references added. Policy statements unchanged.</td>
</tr>
</tbody>
</table>

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### September 2019

**Action:** Replace policy

**Description:** Policy updated with literature review through May 29, 2019; references added. Indication 4 (KRAS, NRAF, and BRAF variant analysis using circulating tumor DNA or circulating tumor cell testing [liquid biopsy] to guide treatment) removed from policy 2.01.141 and inserted here. Policy statement for Indication 4 added: “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.” Title changed to include liquid biopsy.

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