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 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 to predict nonresponse to anti-EGFR monoclonal antibody therapy.

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 medially 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 medially 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 medially 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.
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.

**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 variant</td>
<td>Disease-associated change in the DNA sequence</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</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
</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

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

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, including:

“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.”

“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.”

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.

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 treatment, 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-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. Based on the evidence and 2017 independent clinical input, the clinical input supports that the following indication provides a clinically meaningful improvement in the net health outcome and is consistent with generally accepted medical practice:

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

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.2.2018). 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. 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.

American College of Medical Genetics and Genomics
An evidence review published in 2013 by the American College of Medical Genetics and Genomics 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.

American Society of Clinical Oncology
In 2017, American Society of Clinical Oncology along with American Society for Clinical Pathology, College of American Pathologists, and Association for Molecular Pathology published guidelines on molecular biomarkers for the evaluation of colorectal cancer. Table 1 summarizes the relevant guidelines.

<table>
<thead>
<tr>
<th>Table 1. Summary of Recommendations</th>
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<tbody>
<tr>
<td>Guidelines</td>
</tr>
<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</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Type</th>
<th>SOE</th>
<th>QOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>Recommendation</td>
<td>Adequate/inadequate, balance of benefits and harms</td>
<td>Intermediate/low</td>
</tr>
<tr>
<td>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</td>
<td>Recommendation</td>
<td>Adequate/inadequate, balance of benefits and harms</td>
<td>Intermediate/low</td>
</tr>
<tr>
<td>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</td>
<td>Recommendation</td>
<td>Adequate/inadequate, balance of benefits and harms</td>
<td>Intermediate/low</td>
</tr>
<tr>
<td>There is insufficient evidence to recommend BRAF c.1799 p.V600 mutational status as a predictive molecular biomarker for response to anti-EGFR inhibitors</td>
<td>No recommendation</td>
<td>Insufficient, benefits/harms balance unknown</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

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

The American Society of Clinical Oncology updated its provisional clinical opinion (2015) 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.

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.

REFERENCES

3. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). KRAS mutations and epidermal growth factor receptor inhibitor therapy in metastatic colorectal cancer. TEC Assessments 2008;Volume 23:Tab 6. PMID

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POLICY HISTORY

<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, Reference 14 added, policy statements unchanged.</td>
</tr>
<tr>
<td>March 2013</td>
<td>Update 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 2014</td>
<td>Update 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 2015</td>
<td>Update 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>Update 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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