BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Description

BRAF and MEK inhibitors are drugs designed to target a somatic variant in the BRAF gene. The inhibitors were originally developed for patients with advanced melanoma. BRAF encodes a kinase component in the RAF-MEK-ERK signal transduction phosphorylation cascade. Mutated BRAF causes constitutive kinase activity, which is believed to promote oncogenic proliferation. Direct and specific inhibition of the mutated kinase has been shown to retard tumor growth significantly and may improve patient survival.

OBJECTIVE

The objective of this evidence review is to determine whether testing for BRAF pathogenic variants to select treatment improves the net health outcome in individuals with melanoma or with glioma.

POLICY STATEMENT

Testing for BRAF V600 variants in tumor tissue of patients with unresectable or metastatic melanoma may be considered medically necessary to select patients for treatment with Food and Drug Administration-approved BRAF or MEK inhibitors.
Testing for BRAF V600 variants in tumor tissue of patients with resected stage III melanoma may be considered medically necessary to select patients for treatment with Food and Drug Administration-approved BRAF or MEK inhibitors. Testing for BRAF V600 variants for all other patients with melanoma is considered investigational. Testing for BRAF V600 variants in patients with glioma to select patients for targeted treatment is considered investigational.

**POLICY GUIDELINES**

**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>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
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</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 identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
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</table>

<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>
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</table>

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

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**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).

**FDA REGULATORY STATUS**

Table 1 summarizes the targeted treatments approved by the U.S. Food and Drug Administration for patients with melanoma along with the concurrently approved diagnostic tests. The combination agent encorafenib and binimetinib (Array BioPharma) was approved for the treatment of BRAF variant advanced, unresectable, or metastatic melanoma June 2018. The combination agent of dabrafenib and trametinib (GlaxoSmithKline) was approved in May 2018 for adjuvant treatment of BRAF variant, resected, stage III melanoma; the agent had both breakthrough therapy and priority review designations.

**Table 1. FDA-Approved Targeted Treatments for Melanoma and Approved Companion Diagnostic Tests**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indication</th>
<th>FDA Approval of Companion Diagnostic Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vemurafenib (Zelboraf; Roche/Genentech and Plexxikon)</td>
<td>• 2011: treatment of patients with unresectable or metastatic melanoma with BRAF V600 variants</td>
<td>• 2011: cobas 4800 BRAF V600 Mutation Test (Roche)</td>
</tr>
<tr>
<td>Dabrafenib (Tafinlar; GlaxoSmithKline)</td>
<td>• 2013: treatment of patients with unresectable or metastatic melanoma with BRAF V600E variants</td>
<td>• 2013: THxID™ BRAF kit (bioMérieux)</td>
</tr>
<tr>
<td></td>
<td>• 2014: Used in combination with trametinib to treat patients with unresectable or metastatic melanoma with BRAF V600E or V600K variants</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 2018: Used in combination with trametinib for adjuvant treatment of patients with resected stage III melanoma with BRAF V600E or V600K variants</td>
<td></td>
</tr>
<tr>
<td>Trametinib (Mekinist™; GlaxoSmithKline)</td>
<td>• 2013: treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K variants</td>
<td>• 2013: THxID™ BRAF kit (bioMérieux)</td>
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<tr>
<td></td>
<td>• 2014: Used in combination with dabrafenib to treat patients with unresectable or metastatic melanoma with BRAF V600E or V600K variants</td>
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<tr>
<td></td>
<td>• 2018: Used in combination with dabrafenib for adjuvant treatment of patients with resected stage III melanoma with BRAF V600E or V600K variants</td>
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Summary of Evidence

For individuals who have unresectable or metastatic melanoma who receive BRAF gene variant testing to select a treatment with BRAF or MEK inhibitor combination therapy, the evidence includes randomized trials. The relevant outcomes are OS, disease-specific survival, and test accuracy. Randomized phase 3 trials of BRAF inhibitor therapy in patients selected on the basis of BRAF variant testing have shown improvements in OS and progression-free survival. Single-agent BRAF inhibitor treatment compared with nontargeted treatments have shown superior outcomes for most endpoints. Combination BRAF and MEK inhibitor treatment with vemurafenib plus cobimetinib or dabrafenib plus trametinib have shown superior OS compared with vemurafenib or dabrafenib alone. Data showing treatment effects in patients without BRAF variants do not exist; therefore, BRAF variant testing is required to identify patients to whom these trial results apply. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have resected stage III melanoma who receive BRAF gene variant testing to select a treatment with BRAF or MEK inhibitors, the evidence includes randomized trials. The relevant outcomes are OS, disease-specific survival, and test accuracy. One randomized phase 3 trial of BRAF and MEK combination therapy with dabrafenib plus trametinib in patients selected by BRAF variant testing has shown improvements in recurrence-free survival and OS compared with placebo. One randomized phase 3 trial of vemurafenib monotherapy did not find statistically significant differences in disease-free survival in patients with stage IIIC disease. In patients with stage IIC, IIIA, or IIIB disease, median disease-free survival was prolonged with vemurafenib, but this result was considered exploratory. Data showing treatment effects in patients without BRAF variants do not exist; therefore, BRAF variant testing is required to identify patients to whom these trial results apply. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have glioma who receive BRAF gene variant testing to select a treatment with BRAF or MEK inhibitors, the evidence includes small, prospective, uncontrolled studies and case reports. The relevant outcomes are OS, disease-specific survival, and test accuracy. Studies assessing the use of sorafenib in patients with newly diagnosed and recurrent gliomas combined with various other treatments have not shown benefit, although most did not report BRAF V600 variant status. Evaluation of the BRAF and MEK inhibitors vemurafenib, dabrafenib, and trametinib in patients with gliomas has been limited to a phase 2 "basket" study, including eight patients with glioma, as well as case reports and small case series. Early reports have suggested clinical benefit, but confirmatory randomized controlled trials are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

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The National Comprehensive Cancer Network Guidelines for melanoma (v.2.2018) recommends BRAF variant status should be tested "using an FDA-approved [Food and Drug Administration] test or by a facility approved by CLIA [Clinical Laboratory Improvement Amendments] facility." Combination dabrafenib plus trametinib and combination vemurafenib plus cobimetinib therapies have a category 1 recommendation as a preferred regimen for advanced or metastatic melanoma. Vemurafenib and dabrafenib also have category 1 recommendations for advanced or metastatic melanoma. The National Comprehensive Cancer Network also recommends dabrafenib plus trametinib combination therapy as an option for patients with stage III melanoma who have a BRAF V600-activating variant and sentinel lymph node metastasis greater than 1 mm (category 1).

The National Comprehensive Cancer Network (2019) updated the melanoma guidelines to be specific to cutaneous melanoma (v.2.2019). The guidelines state, "for patients with cutaneous melanoma who are without evidence of disease," a mutational analysis of the primary lesion for BRAF is not recommended, "unless required to guide adjuvant or other systemic therapy or consideration of clinical trials." However, for patients who are symptomatic and/or have quickly progressing melanoma, testing for BRAF V600 could be indicated; BRAF/MEK inhibitors have shorter response time compared with checkpoint immunotherapies and may be the preferred treatment.

Network guidelines for central nervous system cancers (v.1.2018) indicate the following on the use of BRAF molecular markers to guide treatment decisions for primary brain cancers: "BRAF V600E tumors may respond to BRAF inhibitors such as vemurafenib, but comprehensive clinical trials are still ongoing." The 2019 update (v.1.2019) includes no new recommendations regarding the use of BRAF gene variant testing.

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

Not applicable.

**Medicare National Coverage**

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**REFERENCES**


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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 and references updated with literature review, Policy statement modified to read “FDA-approved BRAF inhibitors” in place of “vemurafenib”. Added to Policy guidelines: “Currently only vemurafenib has FDA approval for treatment of advanced melanoma”</td>
</tr>
<tr>
<td>December 2012</td>
<td>Replace policy</td>
<td>Policy and references updated with literature review, Policy statement modified to read “FDA-approved BRAF inhibitors” in place of “vemurafenib”. Added to Policy guidelines: “Currently only vemurafenib has FDA approval for treatment of advanced melanoma”</td>
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<td>December 2013</td>
<td>Replace policy</td>
<td>Policy updated with literature review through August 2013, references 10-12, 14-15, 23-26, and 29 added; references 1, 13, and 30 updated. Policy statements modified to read, “Testing for BRAF V600 mutations” in place of “Testing for the BRAF V600 mutation.”</td>
</tr>
<tr>
<td>December 2014</td>
<td>Replace policy</td>
<td>Policy updated with literature review through September 2, 2014, references were updated, and none were added. Policy statements were revised to align with current FDA approved indication, i.e., “unresectable or metastatic” rather than stage IIC or IV.</td>
</tr>
<tr>
<td>September 2017</td>
<td>Replace policy</td>
<td>Policy updated with literature review through April 25, 2017; references 3-7, 19-31, 43-45, 50-51, and 53-65 added. Policy revised with updated genetics nomenclature. Information about additional FDA-approved BRAF inhibitor (nivolumab) added to policy. Policy statements regarding BRAF testing in melanoma unchanged. Information about FDA-approved MEK inhibitor (cobimetinib) added. New policy statement stating BRAF testing in glioma is investigational was added. Policy title changed to “BRAF Gene Mutation Testing to Select Melanoma or Glioma Patients for Targeted Therapy”</td>
</tr>
<tr>
<td>September 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through April 9, 2018; references 36, 38, 41, 44, 50 and 51 added. Policy statements on BRAF testing in unresectable, metastatic melanoma and in glioma unchanged. New policy statement added stating BRAF testing in resected, stage III melanoma is medically necessary. “Mutation” changed to “variant” in policy title.</td>
</tr>
<tr>
<td>September 2019</td>
<td>Replace policy</td>
<td>Policy updated with literature review through April 18, 2019; references added. Policy statements unchanged.</td>
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