FEP 2.04.77 BRAF Gene Mutation Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Effective Date: October 15, 2017  Related Policies: None

BRAF Gene Mutation 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 to be used in 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 significantly tumor growth and may improve patient survival.

FDA REGULATORY STATUS

In August 2011, vemurafenib (Zelboraf®; Roche/Genentech and Plexxikon) and a class III companion diagnostic test, the cobas® 4800 BRAF V600 Mutation Test (Roche), were coapproved by the U.S. Food and Drug Administration (FDA). The cobas® 4800 BRAF V600 test was approved through the premarket approval process as an aid in selecting melanoma patients whose tumors carry BRAF V600 variants for treatment with vemurafenib.32 Vemurafenib is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 variants. Vemurafenib’s prescribing information states that confirmation of the BRAF V600 variants using an FDA-approved test is required to select patients appropriate for therapy.

In May 2013, dabrafenib (Tafinlar®; GlaxoSmithKline) was approved by FDA through the new drug application process for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E variants, as detected by an FDA-approved test. Dabrafenib is specifically not indicated to treat patients with wild-type BRAF melanoma.

In May 2013, trametinib (Mekinist™; GlaxoSmithKline) was approved by FDA through the new drug application process for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K variants, as detected by an FDA-approved test. Trametinib is specifically not indicated to treat patients who previously received BRAF inhibitor therapy.

The companion diagnostic test coapproved for both dabrafenib and trametinib is the THxID™ BRAF kit (bioMérieux). The kit is intended "as an aid in selecting melanoma patients whose tumors carry the BRAF V600E variants for treatment with dabrafenib and as an aid in selecting melanoma patients whose tumors carry the BRAF V600E or V600K variants for treatment with trametinib."

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In January 2014, the combination of dabrafenib (Tafinlar®) and trametinib (Mekinist™; both GlaxoSmithKline) were approved by FDA through the accelerated approval process for the treatment of patients with unresectable or metastatic melanoma with \textit{BRAF} V600E or V600K variants, as detected by an FDA-approved test. Approval was based on response rather than survival outcomes observed in the phase 1/2 trial described next (see Rationale section).\textsuperscript{16,18} Continued approval is contingent on results from a phase 3 trial comparing combination therapy with dabrafenib monotherapy in patients with metastatic or unresectable melanoma.

In December 2015, cobimetinib (Cotellic®; Genentech) was approved by FDA after priority review for the treatment of patients with unresectable or metastatic melanoma with a \textit{BRAF} V600E or V600K variants, in combination with vemurafenib.

\textbf{POLICY STATEMENT}

Testing for \textit{BRAF} V600 variants in tumor tissue of patients with unresectable or metastatic melanoma may be considered \textbf{medically necessary} to select patients for treatment with Food and Drug Administration- approved \textit{BRAF} or MEK inhibitors (see Policy Guidelines section).

Testing for \textit{BRAF} V600 variants for all other patients with melanoma, including but not limited to use in patients with resectable melanoma, is considered \textbf{investigational}.

Testing for \textit{BRAF} V600 variants in patients with glioma to select patients for targeted treatment is considered \textbf{investigational}.

\textbf{POLICY GUIDELINES}

Vemurafenib, dabrafenib, trametinib, and cobimetinib are currently approved by the U.S. Food and Drug Administration (FDA) specifically to treat advanced \textit{BRAF}-variant melanoma. There are no FDA-approved targeted therapies for \textit{BRAF} V600 variant– positive glioma.

FDA-approved \textit{BRAF} testing kits are intended to select melanoma patients for treatment with vemurafenib, dabrafenib, trametinib, and cobimetinib. Prescribing information for these drugs states that confirmation of \textit{BRAF} V600 variants using an FDA-approved test is required for selection of patients with melanoma appropriate for therapy.

Pivotal trials for vemurafenib, dabrafenib, trametinib, and cobimetinib have enrolled patients with unresectable, stage III or IV melanoma.

\textbf{BENEFIT APPLICATION}

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).

\textbf{RATIONALE}

\textbf{Summary of Evidence}

For individuals who have unresectable or metastatic melanoma who receive \textit{BRAF} gene variant testing to select treatment with \textit{BRAF} or MEK inhibitors, the evidence includes studies of analytic validity and
randomized trials. Relevant outcomes are overall survival, disease-specific survival, and test accuracy. Studies of analytic validity have shown that BRAF variant testing kits have high concordance with the reference standard (Sanger sequencing). Randomized phase 3 trials of BRAF inhibitor therapy in patients selected on the basis of BRAF variant testing have shown improvements in overall survival and progression-free survival. Single-agent BRAF inhibitor treatment compared with nontargeted treatments have shown superior outcomes for most end points. Combination BRAF and MEK inhibitor treatment with vemurafenib plus cobimetinib or dabrafenib plus trametinib have shown superior overall survival compared with either 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 glioma who receive BRAF gene variant testing to select treatment with BRAF or MEK inhibitors, the evidence includes small, prospective, uncontrolled studies and case reports. Relevant outcomes are overall survival, 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 1 phase 2 "basket" study, including 8 patients with glioma, 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
National Comprehensive Cancer Network (NCCN) Guidelines for melanoma (v.1.2017) recommend BRAF-targeted therapy “only for patients with V600 mutation of the BRAF gene, as documented by an FDA-approved [Food and Drug Administration] or CLIA-approved [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.

NCCN guidelines for central nervous system cancers (v.1.2016) does not discuss BRAF-targeted therapy for primary brain cancers.

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
34. Blue Cross and Blue Shield Technology Evaluation Center (TEC). Special Report. Companion diagnostics: Tools). 2017 (May 3);

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#### POLICY HISTORY

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<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tbody>
<tr>
<td>March 2012</td>
<td>New</td>
<td>Policy and references updated with literature review, Policy statement modified to read &quot;FDA-approved BRAF inhibitors&quot; in place of &quot;vemurafenib&quot;. Added to Policy guidelines: &quot;Currently only vemurafenib has FDA approval for treatment of advanced melanoma.&quot;</td>
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<tr>
<td>December 2012</td>
<td>Revise Policy</td>
<td>Policy updated with literature review, references updated, and none were added. Policy statements were revised to align with current FDA approved indication, i.e., &quot;unresectable or metastatic&quot; rather than stage IIC or IV.&quot;</td>
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<tr>
<td>December 2013</td>
<td>Revise 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, &quot;Testing for BRAFV600 mutations&quot; in place of &quot;Testing for the BRAFV600 mutation.&quot;</td>
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<tr>
<td>December 2014</td>
<td>Revise 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., &quot;unresectable or metastatic&quot; rather than stage IIC or IV.&quot;</td>
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<tr>
<td>September 2017</td>
<td>Revise 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 &quot;BRAF Gene Mutation Testing to Select Melanoma or Glioma Patients for Targeted Therapy&quot;.</td>
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