Corporate Medical Policy

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

**File Name:** braf_gene_mutation_testing_to_select_melanoma_or_glioma_patients_for_targeted_therapy

**Origination:** 1/2012

**Last CAP Review:** 3/2017

**Next CAP Review:** 3/2018

**Last Review:** 6/2017

**Description of Procedure or Service**

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 significantly retard tumor growth and may improve patient survival.

Overall incidence rates for melanoma have been increasing for at least 30 years; in 2017, there were more than 87,100 new cases. In advanced (Stage 4) melanoma, the disease has spread beyond the original area of skin and nearby lymph nodes. Although only a small proportion of cases are Stage 4 at diagnosis, prognosis is extremely poor; 5-year survival is 15-20%.

For several decades after its approval in 1975, cytotoxic chemotherapy with dacarbazine was considered the treatment standard for systemic therapy, but has disappointingly low response rates of only 15 to 25% and median response durations of 5 to 6 months; less than 5% of responses are complete. Temozolomide has similar efficacy with the exception of a much greater ability to penetrate the central nervous system. Recently immunotherapy with ipilimumab or with checkpoint inhibitors such as pembrolizumab and nivolumab has demonstrated superior efficacy to chemotherapy regardless of BRAF status and is now recommended as one potential first-line treatment of metastatic or unresectable melanoma by the National Comprehensive Cancer Network; the Network no longer recommends cytotoxic chemotherapy for first-line treatment.

Variants in the BRAF kinase gene are common in tumors of patients with advanced melanoma, and result in constitutive activation of a key signaling pathway (the RAF-MEK-ERK [also called MAPK] pathway) that is associated with oncogenic proliferation. In general, 50-70% of melanoma tumors harbor a BRAF variant; of these, 80% are positive for BRAF^{V600E} and 16% are positive for BRAF^{V600K}. Thus, approximately 45-60% of advanced melanoma patients may respond to a BRAF inhibitor targeted to this mutated kinase.

Two BRAF inhibitors and 2 MEK inhibitors have been developed for use in patients with advanced melanoma. Vemurafenib (trade name Zelboraf®, also known as PLX4032 and RO5185426) was co-developed under an agreement between Roche (Genentech) and Plexxikon. Vemurafenib was developed using a fragment-based, structure-guided approach that allowed the synthesis of a compound with high potency to inhibit the BRAF^{V600E} mutated kinase, and significantly lower potency to inhibit most of many other kinases tested. Preclinical studies demonstrated that vemurafenib selectively blocked the RAF/MEK/ERK pathway in BRAF mutant cells and caused regression of BRAF mutant human melanoma xenografts in murine
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models. Paradoxically, preclinical studies also showed that melanoma tumors with the BRAF wild type gene sequence could respond to mutant BRAF-specific inhibitors with accelerated growth, suggesting that it might be harmful to administer BRAF inhibitors to patients with BRAF wild type melanoma tumors. Potentiated growth in BRAF wild type tumors has not yet been confirmed in melanoma patients as the supportive clinical trials were enrichment trials, enrolling only those patients with tumors positive for the BRAF V600E variant.

Dabrafenib (trade name Tafinlar®, also known as GSK2118436 or SB-590885) is a BRAF inhibitor developed by GlaxoSmithKline (GSK). Dabrafenib inhibits several kinases, including mutated forms of BRAF kinase, with greatest activity against V600E-mutated BRAF. In vitro and in vivo studies demonstrated dabrafenib’s ability to inhibit growth of BRAF V600-mutated melanoma cells.

Trametinib (trade name Mekinist™) is an inhibitor of mitogen-activated extracellular signal-regulated kinase 1 (MEK1) and MEK2 developed by GSK. MEK kinases regulate extracellular signal-related kinase (ERK), which promotes cellular proliferation. BRAF V600E and V600K variants result in constitutive activation of MEK1 and MEK2. Trametinib inhibits growth of BRAF V600 variant-positive melanoma cells in vitro and in vivo.

Cobimetinib is a MEK1 and MEK2 inhibitor. Coadministration of cobimetinib and vemurafenib has resulted in increased apoptosis and reduced tumor growth of BRAF V600E tumor cells in vitro and cobimetinib has prevented vemurafenib-mediated growth of a wild-type BRAF tumor cells in vivo.

Glioma
More than 79,000 new cases of primary malignant and nonmalignant brain and other central nervous system tumors are expected to be diagnosed in the United States in 2017, the majority of which are gliomas. Gliomas encompass a heterogeneous group of tumors and classification of gliomas has changed over time. In 2016, the World Health Organization (WHO) updated its classification of gliomas based on both histopathologic appearance and molecular parameters. The classification ranges from grade I to IV, corresponding to the degree of malignancy (aggressiveness), with WHO grade I being least aggressive and grade IV being most aggressive.

Treatment
Low-grade gliomas were historically classified as WHO grade I or II and include pilocytic astrocytoma, diffuse astrocytoma, and oligodendroglioma. Surgical resection of the tumor is generally performed, although additional therapy with radiation and chemotherapy following surgery is usually required, except for pilocytic astrocytoma. The optimal timing of additional therapies is unclear. Many patients will recur following initial treatment, with a clinical course similar to high-grade glioma. High-grade gliomas (WHO grade III/IV) include anaplastic gliomas and glioblastoma. Maximal surgical resection is the initial treatment followed by combined adjuvant chemoradiotherapy. Temozolomide, an oral alkylating agent, is considered standard systemic chemotherapy for malignant gliomas. The prognosis for patients with high-grade gliomas is poor; the 1-year survival in U.S. patients with anaplastic astrocytoma is about 63% and with glioblastoma is about 38%.

There is a high frequency of BRAF V600E variants in several types of gliomas. For example, BRAF V600E variants have been found in 5% to 10% of pediatric diffusely infiltrating gliomas, 10% to 15% of pilocytic astrocytoma, 20% of ganglioglioma, and more than 50% of pleomorphic xanthoastrocytoma. However, it may be rare in adult glioblastoma. There is considerable interest in targeted therapies that inhibit the MAPK pathway, particularly in patients with high-grade glioma and low-grade gliomas whose tumors are in locations that prevent full resection or recurrent. Evidence from early phase trials in patients with BRAF variant-positive melanoma with brain metastases suggest some efficacy for brain tumor response with vemurafenib and dabrafenib indicating that these agents might be potential therapies for primary brain tumors.
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**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 \textit{BRAF} V600 variants for treatment with vemurafenib. Vemurafenib is indicated for the treatment of patients with unresectable or metastatic melanoma with \textit{BRAF} V600 variants. Vemurafenib’s prescribing information states that confirmation of the \textit{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 \textit{BRAF} V600E variants, as detected by an FDA-approved test. Dabrafenib is specifically not indicated to treat patients with wild-type \textit{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 \textit{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 co-approved for both dabrafenib and trametinib is the THxID™ BRAF Kit manufactured by bioMérieux. The kit is intended “as an aid in selecting melanoma patients whose tumors carry the \textit{BRAF} V600E variants for treatment with dabrafenib and as an aid in selecting melanoma patients whose tumors carry the \textit{BRAF} V600E or V600K variants for treatment with trametinib.”

In January 2014, FDA granted accelerated approval to dabrafenib and trametinib 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 ½ trial. 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.

**Related Policy**

Genetic Testing for Colon Cancer

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

**Policy**

BCBSNC will provide coverage for BRAF Gene Mutation Testing when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

**Benefits Application**

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.
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**When BRAF Gene Mutation Testing is covered**

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 FDA-approved BRAF or MEK inhibitors (see Policy Guidelines).

**When BRAF Gene Mutation Testing is not covered**

Testing for the BRAF V600 variants for all other patients with melanoma, including but not limited to, use in patients with resectable melanoma, is considered investigational.

Testing for BRAF V600 variants in patients with glioma to select patients for targeted treatment is considered investigational.

**Policy Guidelines**

Currently only vemurafenib, dabrafenib, trametinib, and cobimetinib are FDA approved specifically for the treatment of advanced BRAF variant melanoma. There are no FDA-approved targeted therapies for BRAF V600 variant-positive glioma.

FDA-approved BRAF testing kits are intended to select melanoma patients for treatment with vemurafenib, dabrafenib, trametinib, and cobimetinib. There are also commercial labs that perform BRAF testing using non-FDA approved testing. Prescribing information for these drugs states that confirmation of the $BRAF^{V600E}$ variants using an FDA-approved test is required for selection of patients with melanoma appropriate for therapy.

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

For individuals who have unresectable or metastatic melanoma who receive BRAF gene variant testing to select treatment with 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.
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GENETICS NOMENCLATURE UPDATE

Human Genome Variation Society (HGVS) 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. HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUman Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81210, 81406

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

For Policy Titled: BRAF Gene Mutation Testing to Select Melanoma Patients for BRAF Inhibitor Therapy


Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Vermurafenib (Zelboraf™). TEC Specialty Pharmacy Reports 2011; #11-2011.


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For Policy Titled: BRAF Gene Mutation Testing to Select Melanoma or Glioma Patients for Targeted Therapy
Senior Medical Director review 6/2017

Policy Implementation/Update Information

For Policy Titled: BRAF Gene Mutation Testing to Select Melanoma Patients for BRAF Inhibitor Therapy

2/7/12 New policy developed. Testing for the BRAFV600E mutation in tumor tissue of patients with stage IIIC or IV melanoma may be considered medically necessary to select patients for treatment with vemurafenib. Testing for the BRAFV600E mutation for all other indications, including but not limited to, use in patients with lesser stage melanoma, or with non-melanoma tumors, is considered investigational. Medical Director review 1/2012. (mco)

12/11/12 Description section updated. “When Covered” section revised to state: “Testing for the BRAF V600E mutation in tumor tissue of patients with stage IIIC or IV melanoma may be considered medically necessary to select patients for treatment with FDA-approved BRAF inhibitors.” Policy Guidelines updated. New statement added to Policy Guidelines: “Currently only vemurafenib has FDA approval for treatment of advanced melanoma.” Added CPT code 81406 to Billing/Coding section. References updated. Medical Director review 11/2012. (mco)

4/16/13 Specialty Matched Consultant Advisory Panel review 3/20/2013. Regulatory Status added to Description section. No change to policy intent. (btw)

8/27/13 Statement in the When Not Covered section changed from “Testing for the BRAFV600E mutation for all other indications, including but not limited to, use in patients with lesser stage melanoma, or with non-melanoma tumors, is considered investigational.” to “Testing for the BRAFV600 mutation for all other patients with
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melanoma, including but not limited to, use in patients with lesser stage melanoma, is considered investigational.” (btw)

1/28/14 Description and Policy Guidelines sections updated. No change to policy intent. Medical Director review 1/10/2014. Reference added. (btw)


11/25/14 Description section and policy guidelines updated. Statements in When Covered section revised to align with current FDA approved indication “unresectable or metastatic” rather than “stage IIIC or IV.” No change to policy statements. Reference added. (lpr)

4/28/15 Specialty Matched consultant advisory panel review 3/25/2015. No change to policy intent. (lpr)

4/29/16 Updated Description and Policy Guidelines sections. Reference added. Specialty Matched Consultant Advisory Panel review 3/30/2016. No change to policy intent. (lpr)

4/28/17 Updated Description section. Reference added. Specialty Matched Consultant Advisory Panel review 3/29/2017. No change to policy statement. (lpr)

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