Medical Policy

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

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- Policy: Medicare
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**Policy Number: 398**
BCBSA Reference Number: 2.04.77
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

**Related Policies**
Genetic Testing for Lynch Syndrome and Other Inherited Intestinal Polyposis Syndromes, #226

**Policy**

**Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity**

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**.

**Medicare HMO BlueSM and Medicare PPO BlueSM Members**

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the link below.

Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at [https://www.cms.gov](https://www.cms.gov).
Prior Authorization Information

Inpatient
- For services described in this policy, precertification/preauthorization is required for all products if the procedure is performed inpatient.

Outpatient
- For services described in this policy, see below for products where prior authorization might be required if the procedure is performed outpatient.

<table>
<thead>
<tr>
<th>Outpatient</th>
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<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>Prior authorization is not required.</td>
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<tr>
<td>Commercial PPO and Indemnity</td>
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<td>Medicare HMO Blue℠</td>
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<td>Medicare PPO Blue℠</td>
<td>Prior authorization is not required.</td>
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CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>81210</td>
<td>BRAF Raf proto-oncogene, serine/threonine kinase (eg, colon cancer, melanoma), gene analysis, V600 variant(s)</td>
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Description

MELANOMA

Overall incidence rates for melanoma have been increasing for at least 30 years; in 2017, there were more than 87,100 new cases.¹ In advanced (stage IV) melanoma, the disease has spread beyond the original area of skin and nearby lymph nodes. Although only a small proportion of cases are stage IV at diagnosis, the prognosis is extremely poor; 5-year survival is 15% to 20%.

Treatment

Unresectable or Metastatic Melanoma

For several decades after its approval in 1975, cytotoxic chemotherapy with dacarbazine was considered the standard systemic therapy but has provided disappointingly low response rates of only 15% to 25% and median response duration of 5 to 6 months; less than 5% of responses are complete.² Temozolomide has similar efficacy and, unlike dacarbazine, has much better efficacy with central nervous system tumors. Recently immunotherapy with ipilimumab or with checkpoint inhibitors such as pembrolizumab and nivolumab has demonstrated superior efficacy to chemotherapy³⁶ regardless of BRAF status and is now recommended as a potential first-line treatment of metastatic or unresectable melanoma.

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 (RAF-MEK-ERK pathway) that is associated with oncogenic proliferation. In general, 50% to 70% of melanoma tumors harbor a BRAF variant; of these, 80% are positive for the BRAF V600E variant, and 16% are positive for BRAF V600K.⁶ Thus, 45% to 60% of advanced melanoma patients may respond to a BRAF inhibitor targeted to this mutated kinase.
Two BRAF inhibitors (vemurafenib, dabrafenib) and 2 MEK inhibitors (trametinib, cobimetinib) have been developed for use in patients with advanced melanoma. Vemurafenib (also known as PLX4032 and RO5185426) 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 with significantly lower potency to inhibit most of many other kinases tested. Preclinical studies have 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 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 may 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, because the supportive clinical trials were enrichment trials, enrolling only patients with tumors positive for the BRAF V600E variant.

Dabrafenib (also known as GSK2118436 or SB-590885) inhibits several kinases, including mutated forms of the BRAF kinase, with the greatest activity against V600E-mutated BRAF. In vitro and in vivo studies have demonstrated dabrafenib’s ability to inhibit the growth of BRAF V600-variant melanoma cells.

Trametinib is an inhibitor of mitogen-activated extracellular signal-regulated kinase 1 (MEK1) and MEK2. MEK kinases regulate the extracellular signal-related kinase, which promotes cellular proliferation. BRAF V600E and V600K variants result in constitutive activation of MEK1 and MEK2. Trametinib inhibits the 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 the vemurafenib-mediated growth of a wild-type BRAF tumor cells in vivo.

Resected Stage III Melanoma

Wide local excision is the definitive surgical treatment of melanoma. Following surgery, patients with American Joint Committee on Cancer stage III melanoma may receive adjuvant therapy. Ipilimumab, a monoclonal antibody targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4), has been shown to prolong recurrence-free survival by approximately 25% compared with placebo at a median of 5.3 years in patients who had resected stage III disease. Nivolumab, a programmed cell death protein 1 blocking antibody, has been shown to further prolong survival compared with ipilimumab by approximately 35% at 18 months. Before the development of checkpoint inhibitor immunotherapy and targeted therapy, high-dose interferon alfa was an option for adjuvant treatment of stage III melanoma. Interferon alfa has demonstrated an improvement in overall survival but with numerous serious side effects.

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 are 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 radiotherapy 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%.24

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.25-30 However, it may be rare in adult glioblastoma.31

There is considerable interest in targeted therapies that inhibit the RAF-MEK-ERK pathway, particularly in patients with high-grade and low-grade gliomas whose tumors are in locations that prevent full resection. Evidence from early-phase trials in patients with BRAF variant-positive melanoma with brain metastases has suggested some efficacy for brain tumor response with vemurafenib and dabrafenib,32,33 indicating that these agents might be potential therapies for primary brain tumors.

Summary
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.

For individuals who have unresectable or metastatic melanoma who receive BRAF gene variant testing to select treatment with BRAF or MEK inhibitor combination therapy, the evidence includes randomized trials. Relevant outcomes are overall survival, 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 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 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 treatment with BRAF or MEK inhibitors, the evidence includes randomized trials. Relevant outcomes are overall survival, 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 overall survival 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 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 a phase 2 “basket” study, including 8 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.

**Policy History**

<table>
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<td>6/2016</td>
<td>BCBSA National medical policy review. Information about additional FDA-approved BRAF inhibitor (nivolumab) added to policy. 6/1/2016</td>
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<td>1/2016</td>
<td>New references added from BCBSA National medical policy.</td>
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<td>1/2016</td>
<td>Clarified coding information.</td>
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<td>11/2015</td>
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<tr>
<td>6/2015</td>
<td>Local Coverage Determination (LCD): Molecular Diagnostic Tests (MDT) (L33541) added.</td>
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<tr>
<td>12/2014</td>
<td>BCBSA National medical policy review. Policy statements clarified to align with current FDA-approved indication, ie, “unresectable or metastatic” rather than “stage IIIC or IV.” Effective 12/1/2014.</td>
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<tr>
<td>6/2014</td>
<td>Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.</td>
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<td>11/2013</td>
<td>New references from BCBSA National medical policy.</td>
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<tr>
<td>11/1/12</td>
<td>New policy describing ongoing coverage and non-coverage.</td>
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**Information Pertaining to All Blue Cross Blue Shield Medical Policies**

Click on any of the following terms to access the relevant information:

- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

**References**


