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

Policy # 00320  
Original Effective Date: 11/16/2011  
Current Effective Date: 08/14/2019

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage  
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider testing for BRAF V600 variants in tumor tissue of patients with unresectable or metastatic melanoma to select patients for treatment with Food and Drug Administration (FDA) approved BRAF or MEK inhibitors to be eligible for coverage.**

Based on review of available data, the Company may consider testing for testing for BRAF V600 variants in tumor tissue of patients with resected stage III melanoma to select patients for treatment with Food and Drug Administration (FDA) approved to be eligible for coverage.**

When Services Are Considered Investigational  
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers testing for BRAF V600 variants for all other patients with melanoma to be investigational.*

Based on review of available data, the Company considers testing for BRAF V600 variants in patients with glioma to select patients for targeted treatment to be 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 PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous Definition</th>
<th>Updated Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td></td>
</tr>
<tr>
<td>Disease-associanted variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</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>
</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>
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ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

**Background/Overview**

**Melanoma**

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 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. 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 chemotherapy, 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. 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. Co-administration 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 oligodendrogliaoma. 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%.

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.
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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 indicating that these agents might be potential therapies for primary brain tumors.

**FDA or Other Governmental Regulatory Approval**

**U.S. Food and Drug Administration (FDA)**

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) is under review for the treatment of BRAF variant advanced, unresectable, or metastatic melanoma with target action date of June 30, 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 3. FDA-Approved Targeted Treatments for Melanoma and Their Approved Companion Diagnostic Tests

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indication</th>
<th>FDA Approval of Companion Diagnostic Test</th>
</tr>
</thead>
</table>
| Vemurafenib (Zelboraf®; Roche/Genentech and Plexxikon) | • 2011: treatment of patients with unresectable or metastatic melanoma with BRAF V600 variants | • 2011: cobas® 4800 BRAF V600 Mutation Test (Roche)  
  • 2017: FoundationOne CDx™ (Foundation Medicine) |
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<table>
<thead>
<tr>
<th>Drug</th>
<th>Year(s)</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabrafenib</strong> (Tafinlar&lt;sup&gt;®&lt;/sup&gt;; 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>• 2017: FoundationOne CDx™ (Foundation Medicine)</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><strong>Trametinib</strong> (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>
</tr>
<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>
<td>• 2017: FoundationOne CDx™ (Foundation Medicine)</td>
</tr>
<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>
<td></td>
</tr>
<tr>
<td><strong>Cobimetinib</strong> (Cotellic™; Genentech)</td>
<td>• 2015: Used in combination with vemurafenib to treat patients with unresectable or metastatic melanoma with a BRAF V600E or V600K variants</td>
<td>• 2017: FoundationOne CDx™ (Foundation Medicine)</td>
</tr>
</tbody>
</table>

FDA: Food and Drug Administration.
FDA product code: OWD.
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**Rationale/Source**
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 non-targeted 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 IIC 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.
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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.

Supplemental Information
Practice Guidelines and Position Statements
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).

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.”

U.S. Preventive Services Task Force Recommendations
Not applicable.
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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.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>A 2-part Phase III Randomized, Open Label, Multicenter Study of LGX818 Plus MEK162 Versus Vemurafenib and LGX818 Monotherapy in Patients With Unresectable or Metastatic BRAF V600 Mutant Melanoma (COLUMBUS)</td>
<td>921</td>
<td>Mar 2019</td>
</tr>
<tr>
<td>NCT01909453</td>
<td>A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Vemurafenib (RO5185426) Adjuvant Therapy in Patients With Surgically Resected, Cutaneous BRAF Mutant Melanoma at High Risk for Recurrence</td>
<td>475</td>
<td>Oct 2020</td>
</tr>
<tr>
<td>NCT01667419</td>
<td>A Randomized Phase III Trial of Dabrafenib + Trametinib Followed by Ipilimumab + Nivolumab at Progression vs. Ipilimumab + Nivolumab Followed by Dabrafenib + Trametinib at Progression in Patients With Advanced BRAFV600 Mutant Melanoma</td>
<td>300</td>
<td>Oct 2022</td>
</tr>
<tr>
<td>NCT02224781</td>
<td>COMBI-AD: A Phase III Randomized Double Blind Study of Dabrafenib (GSK2118436) in COMBInation With Trametinib (GSK1120212) Versus Two Placebos in the ADjuvant Treatment of</td>
<td>852</td>
<td>Mar 2023</td>
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</table>
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<table>
<thead>
<tr>
<th><strong>Glioma</strong></th>
<th><strong>High-risk BRAF V600 Mutation-positive Melanoma After Surgical Resection</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NCT01089101</strong></td>
<td>A Phase I and Phase II and Re-Treatment Study of AZD6244 for Recurrent or Refractory Pediatric Low Grade Glioma</td>
<td>180</td>
<td>Dec 2018</td>
</tr>
<tr>
<td><strong>NCT01748149</strong></td>
<td>PNOC-002: Safety, Phase 0, and Pilot Efficacy Study of Vemurafenib, an Oral Inhibitor of BRAFV600E, in Children and Young Adults With Recurrent/Refractory BRAFV600E- or BRAF Ins T Mutant Brain Tumors</td>
<td>54</td>
<td>Jun 2019</td>
</tr>
<tr>
<td><strong>NCT01677741</strong></td>
<td>Phase I/IIa, 2-Part, Multi-Center, Single-Arm, Open-Label Study to Determine the Safety, Tolerability and Pharmacokinetics of Oral Dabrafenib in Children and Adolescent Subjects With Advanced BRAF V600-Mutation Positive Solid Tumors</td>
<td>86</td>
<td>Sep 2019</td>
</tr>
<tr>
<td><strong>NCT02285439</strong></td>
<td>Phase I Study of MEK162 for Children With Progressive or Recurrent Cancer and a Phase II Study for Children With Low-Grade Gliomas and Other Ras/Raf/MAP Pathway Activated Tumors</td>
<td>80</td>
<td>Jun 2020</td>
</tr>
<tr>
<td><strong>NCT02034110</strong></td>
<td>A Phase II, Open-label, Study in Subjects With BRAF V600E-Mutated Rare Cancers With Several Histologies to Investigate the Clinical Efficacy and Safety of the Combination Therapy of Dabrafenib and Trametinib</td>
<td>225</td>
<td>Aug 2020</td>
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<tr>
<td><strong>NCT02465060</strong></td>
<td>Molecular Analysis for Therapy Choice (MATCH)</td>
<td>6452</td>
<td>Jun 2022</td>
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<tr>
<td><strong>NCT02684058</strong></td>
<td>Phase II Open-label Global Study to Evaluate the Effect of Dabrafenib in Combination With Trametinib in Children and Adolescent Patients With BRAF V600 Mutation Positive Low Grade Glioma (LGG) or Relapsed or Refractory High Grade Glioma (HGG)</td>
<td>142</td>
<td>Sep 2024</td>
</tr>
</tbody>
</table>
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| NCT02684058 | Phase II Open-label Global Study to Evaluate the Effect of Dabrafenib Treatment in Children and Adolescent Patients With BRAF V600 Mutation Positive Relapsed or Refractory High Grade Glioma (HGG) | 142 | Sep 2024 |
| NCT03155620 | NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol | 1500 | Sep 2027 |

NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.

References
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35. Food and Drug Administration. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). 2018 (April 27);
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11/03/2011 Medical Policy Committee review
11/01/2012 Medical Policy Committee review
12/12/2013 Medical Policy Committee review
12/18/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2015 Coding Update
01/08/2015 Medical Policy Committee review
01/21/2015 Medical Policy Implementation Committee approval. New policy.
01/07/2016 Medical Policy Committee review
01/22/2016 Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
01/05/2017 Medical Policy Committee review
01/18/2017 Medical Policy Implementation Committee approval. No change to coverage.
10/05/2017 Medical Policy Committee review

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10/18/2017 Medical Policy Implementation Committee approval. Policy revised with updated genetics nomenclature. 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”.

08/09/2018 Medical Policy Committee review
08/15/2018 Medical Policy Implementation Committee approval. New policy statement added stating BRAF testing in resected, stage III melanoma is eligible for coverage. “Mutation” changed to “variant” in policy title.

08/01/2019 Medical Policy Committee review
08/14/2019 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 08/2020

Coding

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contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
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<tr>
<td>HCPCS</td>
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<td>ICD-10 Diagnosis</td>
<td>C43.0-C43.9, D03.0-D03.9</td>
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</tbody>
</table>

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment,
BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320
Original Effective Date: 11/16/2011
Current Effective Date: 08/14/2019

would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.