Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Melanoma or Glioma

Policy #  00320
Original Effective Date:  11/16/2011
Current Effective Date:  01/01/2023

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.

Note: Genetic Testing for Lynch Syndrome and Other Inherited Colon is addressed separately in medical policy 00190.

Note: Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies is addressed separately in medical policy 00423.

Note: Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer is addressed separately in medical policy 00452.

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 initial testing for BRAF V600 variants in tumor tissue of individuals with unresectable or metastatic melanoma to select patients for treatment with Food and Drug Administration (FDA) approved therapy (e.g., BRAF inhibitors, MEK inhibitors, or immunotherapy) to be eligible for coverage.**

Based on review of available data, the Company may consider initial 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 BRAF or MEK inhibitors to be eligible for coverage.**
Based on review of available data, the Company may consider tumor testing for NTRK gene fusion in individuals with metastatic or unresectable melanoma or glioma, who progressed following standard of care or failed standard of care treatment, to select patients for treatment with Food and Drug Administration (FDA) approved therapy (e.g., larotrectinib or entrectinib) to be eligible for coverage.**

Based on review of available data, the Company may consider initial testing for BRAF V600 variants in tumor tissue of individuals with unresectable or metastatic glioma who have progressed following prior treatment and have no satisfactory alternative treatment options to select Food and Drug Administration (FDA) approved treatment (e.g., dabrafenib-trametinib combination) to be eligible for coverage.**

Testing for other variants may become available between policy updates (see Policy Guidelines).

Notes:
Molecular testing for detection of IDH 1 and 2, ATRX and TERT promoter variants in all gliomas, and MGMT promoter methylation for all high-grade gliomas (grade 3 and 4) can be considered to improve diagnostic accuracy and prognostic stratification that may inform treatment selection.

For 5 or more gene tests being run on the same platform, such as multi-gene panel next generation sequencing (NGS), single available procedure code for the multi-gene panel test is to be utilized.

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 and NTRK variants in all other situations, including but not limited to repeat tumor tissue testing (unless larger more representative tumor sample is available if concern for sampling error) and circulating tumor DNA testing (ct-DNA or liquid biopsy), to be investigational.*
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Based on review of available data, the Company considers testing for other variants and/or tumor mutational burden (TMB) in patients with melanoma or glioma to select patients for treatment with Food and Drug Administration-approved immunotherapy to be investigational.*

**Policy Guidelines**

Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies is addressed separately in medical policy 00423.

Testing for individual genes (not gene panels) associated with FDA-approved therapeutics (ie, as companion diagnostic tests) for therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher are not subject to extensive evidence review. Note that while the FDA approval of companion diagnostic tests for genes might include tests that are conducted as panels, the FDA approval is for specific genes (such as driver mutations) and not for all of the genes on the test panel.

For guidance on testing criteria between policy updates, refer to the FDA's List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) (https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools) for an updated list of FDA-approved tumor markers and consult the most current version of National Comprehensive Cancer Network (NCCN) management algorithms.

**Background/Overview**

**Melanoma**

Overall incidence rates for melanoma have been increasing for at least 30 years. 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%.
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Variants in the b-raf proto-oncogene, serine/threonine kinase (BRAF) kinase gene are common in tumors of patients with advanced melanoma and result in constitutive activation of a key signaling pathway (rapidly accelerated fibrosarcoma [RAF]-MEK-extracellular signal-regulated kinase [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.

BRAF inhibitors (e.g., vemurafenib, dabrafenib) and mitogen-activated protein kinase (MEK) inhibitors (e.g., 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 cells3,4,5, and caused regression of BRAF mutant human melanoma xenografts in murine models.2, 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.

Neurotrophic tyrosine receptor kinase (NTRK) gene fusions are uncommon kinase fusion events that drive tumorigenesis in a small fraction of solid tumors, regardless of tissue type. The tropomyosin receptor kinases (TRK) proteins A, B, and C are encoded by the genes NTRK1, NTRK2, and NTRK3 respectively. In healthy tissue, the TRK pathway is involved in the development and functioning of the nervous system as well as cell survival. Chromosomal rearrangements involving in-frame fusions of these genes with various partners can result in constitutively-activated chimeric TRK fusion proteins that are oncogenic, promoting tumor cell proliferation and their survival. Larotrectinib and entrectinib are kinase inhibitors of TRK A, B, and C protein. However, entrectinib additionally inhibits 2 other kinases: anaplastic lymphoma kinase and proto-oncogene tyrosine-protein kinase.

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The annual incidence of NTRK fusion-driven tumors is estimated to be 1,500 to 5,000 cases in the United States. NTRK fusions may be more characteristic of rare cancers such as mammary analogue secretory carcinoma, secretory breast carcinoma, or infantile fibrosarcoma. The incidence of NTRK fusions is below 1% for most common cancers such as melanoma.

**Glioma**

Gliomas encompass a heterogeneous group of tumors and the 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.

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 have suggested some efficacy for brain tumor response with vemurafenib and dabrafenib indicating that these agents might be potential therapies for primary brain tumors.

The incidence of NTRK fusions ranges from 10.3% in patients with high-grade gliomas to <1% in low-grade gliomas.

**Tumor Mutational Burden**

Tumor mutational burden (TMB), a measure of gene mutations within cancer cells, is an emerging biomarker of outcomes with immunotherapy in multiple solid tumor types. Initially, assessments of TMB involved whole exome sequencing (WES). More recently, targeted next-generation sequencing (NGS) panels are being adapted to estimate TMB. Currently FoundationOne CDx is the only FDA-approved panel for estimating TMB, but others are in development.
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**FDA or Other Governmental Regulatory Approval**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of these tests.

Table 1 summarizes the targeted treatments approved by the FDA for patients with melanoma along with the concurrently approved diagnostic tests as of the most recent policy update.

The FDA maintains a regularly updated list of 'Cleared or Approved Companion Diagnostic Devices'. New tests may become available between policy updates.

**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>Pembrolizumab (Keytruda®; Merck)</td>
<td>• 2020: treatment of adult and pediatric patients with unresectable or metastatic tumor mutation burden-high (TMB-H) [≥10 mutations/megabase] solid tumors, that have progressed following prior treatment and who have no satisfactory treatment options</td>
<td>• 2020: FoundationOne CDx™ (Foundation Medicine)</td>
</tr>
<tr>
<td>Atezolizumab (Tecentriq®; Genentech)</td>
<td>• 2020: treatment of patients with unresectable or metastatic melanoma with (BRAF\ V600) variants in combination with cobimetinib and vemurafenib</td>
<td>For cobimetinib in combination with vemurafenib: • 2016: cobas® 4800 (BRAF\ V600)</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
<th>Companion Diagnostic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entrectinib (Rozytrek®; Genentech)</td>
<td>2019: treatment of adults and pediatric patients 12 years of age and older with solid tumors that have a NTRK gene fusion without a known acquired resistance mutation, that are metastatic or where surgical treatment is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory standard therapy</td>
<td>No FDA-approved companion diagnostic</td>
</tr>
<tr>
<td>Larotrectinib (Vitrakvi®; Loxo Oncology/Bayer)</td>
<td>2018: treatment of adult and pediatric patients with solid tumors that have a NTRK gene fusion without a known acquired resistance mutation, that are metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment</td>
<td>2020: FoundationOne CDx™ (Foundation Medicine)</td>
</tr>
<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>
</tbody>
</table>
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| Dabrafenib (Tafinlar®; GlaxoSmithKline) | 2013: treatment of patients with unresectable or metastatic melanoma with **BRAF** V600E  
2014: Used in combination with trametinib to treat patients with unresectable or metastatic melanoma with **BRAF** V600E or V600K variants  
2018: Used in combination with trametinib for adjuvant treatment of patients with resected stage III melanoma with **BRAF** V600E or V600K variants  
2022: Used in combination with trametinib for adults and children 6 years of age or older with **BRAF** V600E-positive unresectable or metastatic solid tumor who have progressed following prior treatment and have no satisfactory alternative treatment options.  
Drug combination is not indicated for patients with colorectal cancer because of known intrinsic resistance to **BRAF** inhibitors. | 2017: FoundationOne CDx™ (Foundation Medicine)  
2013: THxID™ BRAF kit (bioMérieux)  
2017: FoundationOne CDx™ (Foundation Medicine) |
| Trametinib (Mekinist™; GlaxoSmithKline) | 2013: treatment of patients with unresectable or metastatic melanoma with **BRAF** V600E or V600K variants | 2013: THxID™ BRAF kit (bioMérieux) |
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<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>Used in combination with dabrafenib to treat patients with unresectable or metastatic melanoma with <em>BRAF V600E</em> or <em>V600K</em> variants</td>
</tr>
<tr>
<td>2018</td>
<td>Used in combination with dabrafenib for adjuvant treatment of patients with resected stage III melanoma with <em>BRAF V600E</em> or <em>V600K</em> variant</td>
</tr>
<tr>
<td>2022</td>
<td>Used in combination with dabrafenib to treat adults and children 6 years of age or older with <em>BRAF V600E</em>-positive unresectable or metastatic solid tumor who have progressed following prior treatment and have no satisfactory alternative treatment options. Drug combination is not indicated for patients with colorectal cancer because of known intrinsic resistance to <em>BRAF</em> inhibitors.</td>
</tr>
<tr>
<td>2015</td>
<td>Used in combination with vemurafenib to treat patients with unresectable or metastatic melanoma with a <em>BRAF V600E</em> or <em>V600K</em> variants</td>
</tr>
<tr>
<td>2016</td>
<td>cobas® 4800 <em>BRAF V600</em> Mutation Test (Roche)</td>
</tr>
<tr>
<td>2017</td>
<td>FoundationOne CDx™‡ (Foundation Medicine)</td>
</tr>
</tbody>
</table>

Cobimetinib (Cotellic®‡; Genentech)

- 2015: Used in combination with vemurafenib to treat patients with unresectable or metastatic melanoma with a *BRAF V600E* or *V600K* variants

- 2016: cobas® 4800 *BRAF V600* Mutation Test (Roche)

- 2017: FoundationOne CDx™‡ (Foundation Medicine)
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<table>
<thead>
<tr>
<th>Drug</th>
<th>Approval Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binimetinib (Mektovi®; Array BioPharma)</td>
<td>• 2018: Used in combination with encorafenib to treat patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation.</td>
</tr>
<tr>
<td>Encorafenib (Bravtovi®; Array BioPharma)</td>
<td>• 2018: Used in combination with binimetinib to treat patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation.</td>
</tr>
<tr>
<td></td>
<td>• 2013: THxID™ BRAF kit (bioMérieux)</td>
</tr>
</tbody>
</table>

BRAF: b-raf proto-oncogene, serine/threonine kinase; FDA: Food and Drug Administration; NTRK: Neurotrophic tyrosine receptor kinase; PD-L1: programmed death-ligand 1; TRK: tropomyosin receptor kinase.

1. Approved under accelerated approval. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.
2. The safety and efficacy of pembrolizumab in pediatric patients with TMB-H central nervous system cancers have not been established.
3. Eligibility not dependent on PD-L1 status.
4. Please consult the FDA list of 'Cleared or Approved Companion Diagnostic Devices' for most current information.

FDA product code: OWD.

**Rationale/Source**

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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Description
The identification of specific, targetable oncogenic “driver mutations” in a subset of melanomas and gliomas has resulted in a reclassification of solid tumors to include molecular subtypes that may direct targeted therapy depending on the presence of specific variants. B-RAF proto-oncogene, serine/threonine kinase (BRAF) and mitogen-activated protein kinase (MEK) inhibitors, alone or in combination with checkpoint inhibitors, are drugs designed to target a somatic variant in the BRAF gene. BRAF and MEK inhibitors were originally developed for patients with advanced melanoma. BRAF encodes a kinase component in the rapidly accelerated fibrosarcoma (RAF)-MEK-extracellular signal-regulated kinase (ERK) signal transduction phosphorylation cascade. Variants in BRAF cause 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. Checkpoint inhibitors are monoclonal antibodies that were initially developed to target tumors expressing high levels of programmed death-ligand 1 (PD-L1). Tumors with a high tumor mutational burden (TMB) may also predict benefit from checkpoint inhibitor immunotherapy.

Summary of Evidence
For individuals who have unresectable or metastatic melanoma who receive BRAF gene variant testing to select a treatment with BRAF inhibitors, MEK inhibitors, or immunotherapy, the evidence includes randomized trials. Relevant outcomes are overall survival (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 has 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 an 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. Relevant
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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 an 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. 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 "basket" studies. Selumetinib is being investigated in pediatric, low-grade glioma. Confirmatory randomized controlled trials are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have unresectable or metastatic melanoma or glioma who receive TMB testing to select treatment with immunotherapy, the evidence includes a prespecified retrospective subgroup analysis of a nonrandomized phase 2 trial. Relevant outcomes are OS, disease-specific survival, and test accuracy. Objective responses were observed in 35% of participants who had both TMB-high status and PD-L1-positive tumors and in 21% of participants who had TMB-high status and PD-L1-negative tumors. TMB-high status was associated with improved response irrespective of PD-L1 status. Median OS and progression-free survival (PFS) were not significantly different between TMB groups. Patients with melanoma and glioma were not enrolled in the study. Well-designed prospective studies enrolling patients in the population of interest are required. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.
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Additional Information
Extensive evidence review is not included for somatic tests of individual genes (not gene panels) associated with U.S. FDA approved therapeutics (ie, as companion diagnostic tests) for therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher. Note that while the FDA approval of companion diagnostic tests for genes may include tests that are conducted as panels, the FDA approval is for specific genes (such as driver mutations) and not for all of the genes on the test panel.

Supplemental Information
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network
The National Comprehensive Cancer Network (NCCN) guidelines for cutaneous melanoma (v.3.2022) recommends b-raf proto-oncogene, serine/threonine kinase (BRAF) mutation testing for patients with stage IIIB microscopic satellite disease if adjuvant therapy or clinical trial enrollment is being considered. BRAF mutation testing is also recommended for patients who are sentinel node-positive and stage IIIB/C/D and the consideration of BRAF mutation testing for sentinel node-positive stage IIIA. The guidelines recommend BRAF mutation testing for clinically node-positive or clinical satellite/in-transit stage III. For stage IV patients, the guidelines recommend BRAF mutation testing if not previously performed.

The panel does not recommend BRAF or NGS testing for resected stage I-II cutaneous melanoma, unless to inform clinical trial participation. For initial presentation with stage IV disease or clinical
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recurrence, panel recommends obtaining tissue to ascertain alterations in BRAF, and in the appropriate clinical setting, KIT from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy. If BRAF single-gene testing was the initial test performed, and is negative, clinicians should strongly consider larger NGS panels to identify other potential genetic targets (e.g., KIT, BRAF non-V600). It was also noted that utility of PD-L1 biomarker and use of mutation burden requires further investigation. Repeat molecular testing upon recurrence or metastasis is likely to be of low yield, unless new or more comprehensive testing methods are used, or larger, more representative sample is available if concern for sampling error. Repeat testing following progression on targeted therapy (BRAF- or KIT-directed therapy) does not appear to have clinical utility. Guidelines noted that testing on tumor tissue is preferred but may be performed on peripheral blood (liquid biopsy) if tumor tissue is not available.

Network guidelines for central nervous system cancers (v.2.2022) note that there are no identified targeted agents with demonstrated efficacy in glioblastoma. However, the panel encourages molecular testing of tumor because if a driver mutation (such as BRAF V600E-activating mutations, or NTRK fusions) is detected, it may be reasonable to treat with a targeted therapy on a compassionate use basis and/or the patient may have more treatment options in the context of a clinical trial. Molecular testing also has a valuable role in improving diagnostic accuracy and prognostic stratification that may inform treatment selection.

IDH1 and 2, ATRX, TERT promoter mutation testing is required for the workup of all gliomas. MGMT promoter methylation is an essential part of molecular diagnostics for all high-grade gliomas (grade 3 and 4). BRAF fusion and/or mutation testing is recommended in the appropriate clinical context (see above). The guidelines do not discuss tumor mutation burden testing.

NCCN guidelines indicated 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 guidelines state that BRAF...
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and mitogen-activated protein kinase (MEK) inhibitors can be considered for pilocytic astrocytoma, pleomorphic xanthoastrocytoma, or ganglioglioma with a BRAF V600E activating mutation.

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

Medicare National Coverage
In January 2020, the Centers for Medicare and Medicaid Services (CMS) determined that next generation sequencing (NGS) is covered for patients with somatic (acquired) cancer when the diagnostic test is performed in a CLIA-(Clinical Laboratory Improvement Amendments) certified laboratory, when ordered by a treating physician, and when all of the following requirements are met:

a. Patient has:
   i. either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and
   ii. not been previously tested with the same test using NGS for the same cancer genetic content, and
   iii. decided to seek further cancer treatment (eg, therapeutic chemotherapy).

b. The diagnostic laboratory test using NGS must have:
   i. Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,
   ii. an FDA-approved or -cleared indication for use in that patient’s cancer; and,
   iii. results provided to the treating physician for management of the patient using a report template to specify treatment options.

CMS states that local Medicare carriers may determine coverage of next generation sequencing as a diagnostic laboratory test for patients with advanced cancer only when the test is performed in a CLIA-certified laboratory, when ordered by a treating physician, and when the patient meets criteria in (a) above.

Ongoing and Unpublished Clinical Trials
Some currently ongoing or unpublished trials that might influence this review are listed in Table 2.
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Table 2. 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><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Melanoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02553642</td>
<td>A Prospectively Designed Study to Assess the Relationship Between Tumor Mutation Burden and Predicted Neo-antigen Burden in Patients With Advanced Melanoma or Bladder Cancer Treated With Nivolumab or Nivolumab Plus Ipilimumab (CA209-260)</td>
<td>81</td>
<td>Sep 2023</td>
</tr>
<tr>
<td>NCT02967692</td>
<td>A Randomized, Double-blind, Placebo-controlled, Phase III Study Comparing the Combination of PDR001, Dabrafenib and Trametinib Versus Placebo, Dabrafenib and Trametinib in Previously Untreated Patients With Unresectable or Metastatic BRAF V600 Mutant Melanoma (COMBI-i)</td>
<td>569</td>
<td>Jul 2023</td>
</tr>
<tr>
<td>NCT04309409</td>
<td>Adjuvant Nivolumab Treatment in Stage II High-risk Melanoma - A Randomized, Controlled, Phase III Trial With Biomarker-based Risk Stratification (NivoMela)</td>
<td>374</td>
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<td>NCT04722575</td>
<td>NEOadjuvant Plus Adjuvant Therapy With Combination or Sequence of Vemurafenib, cobInetinib, and atezolizuMab in Patients With High-risk, Surgically Resectable BRAF Mutated and Wild-type Melanoma (NEO-TIM)</td>
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**Glioma**
Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy of Melanoma or Glioma

Policy # 00320
Original Effective Date: 11/16/2011
Current Effective Date: 01/01/2023

<table>
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<tr>
<td>NCT01089101</td>
<td>A Phase I and Phase II and Re-Treatment Study of AZD6244 for Recurrent or Refractory Pediatric Low Grade Glioma</td>
<td>220</td>
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<td>NCT01748149</td>
<td>PNOC-002: Safety, Phase 0, and Pilot Efficacy Study of Vemurafenib, an Oral Inhibitor of BRAF V600E, in Children and Young Adults With Recurrent/Refractory BRAFV600E- or BRAF Ins T Mutant Brain Tumors</td>
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<td>NCT02285439</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>
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<td>NCT02465060</td>
<td>Molecular Analysis for Therapy Choice (MATCH)</td>
<td>6452</td>
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<td>NCT03220035</td>
<td>NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice)- Phase 2 Subprotocol of Vemurafenib in Patients With Tumors Harboring BRAF V600 Mutations</td>
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<tr>
<td>NCT02684058</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>150</td>
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<tr>
<td>NCT04166409</td>
<td>A Phase 3 Randomized Non-Inferiority Study of Carboplatin and Vincristine Versus Selumetinib (NSC# 748727) in Newly Diagnosed or Previously Untreated Low-Grade Glioma (LGG) Not Associated With BRAF V600E Mutations or Systemic Neurofibromatosis Type 1 (NF1)</td>
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<td>Dec 2026</td>
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<td>NCT03155620</td>
<td>NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol</td>
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NCT: national clinical trial.
\(^a\) Denotes industry-sponsored or cosponsored trial.

**References**

8. Food and Drug Administration. Center for Drug Evaluation and Research Application Number: 210861orig1s000 and 211710orig1s000: Multi-Discipline Review. 2018; https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210861Orig1s000_211710Orig1s000MultidisciplineR.pdf.
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Policy History
Original Effective Date:  11/16/2011
Current Effective Date:  01/01/2023
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
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.
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08/01/2019 Medical Policy Committee review
08/14/2019 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/06/2020 Medical Policy Committee review
08/12/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/02/2021 Medical Policy Committee review
09/08/2021 Medical Policy Implementation Committee approval. New policy statement stating TMB testing in melanoma and glioma is investigational was added. Policy title changed to "Genetic Testing to Select Melanoma or Glioma Patients for Targeted Therapy."
09/01/2022 Medical Policy Committee review
09/14/2022 Medical Policy Implementation Committee approval. Policy updated with literature review through May 2022; references added. Policy scope revised to exclude extensive review of individual gene testing associated with FDA-approved therapeutics (i.e., as companion diagnostics) for therapies with National Comprehensive Cancer Network recommendations of 2A or higher. Policy guidelines updated and policy statement added to reflect this approach. Minor editorial refinements to policy statements; intent unchanged. Title changed. Coding updated.
11/08/2022 Coding update

Next Scheduled Review Date: 09/2023

Coding
The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®), copyright 2021 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.
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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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<th>Code Type</th>
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<td>CPT</td>
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<td>Adding codes effective 01/01/2023: 81191, 81192, 81193, 81194, 0037U, 81287</td>
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<tr>
<td>HCPCS</td>
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*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...
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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 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, 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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