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: 10/09/2023

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: Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy) is addressed separately in medical policy 00497.

Note: Genetic Testing for Familial Cutaneous Malignant Melanoma is addressed separately in medical policy 00206.

Note: Gene Expression Profiling for Skin Cancer is addressed separately in medical policy 00622.

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, or with resected stage III melanoma to select individuals for treatment with Food and Drug Administration (FDA) approved therapy (e.g., BRAF inhibitors, MEK inhibitors, or immunotherapy) to be **eligible for coverage.****

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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.****

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 treatment or have no satisfactory treatment options to select treatment with Food and Drug Administration (FDA) approved therapy (e.g., larotrectinib or entrectinib) 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 individuals with melanoma or glioma to select individuals for treatment with Food and Drug Administration-approved immunotherapy to be **investigational.***

Policy Guidelines

This policy does not address use of *BRAF* testing for the purpose of Central Nervous System (CNS) tumor diagnosis. As molecular diagnostic tests including *BRAF* might be performed for CNS tumor classification, Plans might need to consult the WHO Classification of Tumors of the CNS or other sources.

This policy on *BRAF* testing varies from National Comprehensive Cancer Network (NCCN)-Pediatric CNS guidelines for pediatric gliomas. Plans might locally consider coverage of *BRAF* V600E testing to inform coverage of vemurafenib.
Testing for other variants may become available between policy updates.

Testing for individual genes (not gene panels) associated with Food and Drug Administration (FDA)-approved therapeutics for therapies with 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.

Note that TMB is often included in panel tests and might not have separate coding; Plans with coverage for panels might consider local decision for TMB.

FDA approves tests in between policy review cycles. As such, newly approved tests might need to be considered per local Plan discretion. 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 NCCN management algorithms.

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Note: Extensive evidence review is not included for somatic tests of individual genes (not gene panels) associated with FDA-approved therapies with NCCN recommendations of 2A or higher. The pivotal evidence is included in Table 1 for informational purposes. Additionally, no evidence review is provided for somatic tests of individual genes that do not have associated FDA-approved therapies (when used off-label).

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%.

Variants in the b-raf proto-oncogene, serine/threonine kinase (BRAF) kinase gene are common in tumors of individuals 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 individuals 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 individuals 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

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BRAF inhibitors to individuals with BRAF wild-type melanoma tumors. Potentiated growth in BRAF wild-type tumors has not yet been confirmed in melanoma individuals, because the supportive clinical trials were enrichment trials, enrolling only individuals 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.

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 2021, the World Health Organization (WHO) updated its classification of gliomas, glioneuronal tumors, and neuronal tumors to divide them into distinct families: 1) adult-type diffuse gliomas (the majority of primary brain tumors in adults), 2) pediatric-type diffuse low-grade gliomas (expected to have good prognoses), 3) pediatric-type diffuse high-grade gliomas (expected to behave aggressively, 4) circumscribed astrocytic gliomas (referring to their more solid growth pattern as opposed to diffuse tumors), 5) glioneuronal and neuronal tumors (a diverse group of tumors, featuring neuronal differentiation), and 6) ependymal tumors (classified by site as well as histological and molecular features).

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There is considerable interest in targeted therapies that inhibit the RAF-MEK-ERK pathway, particularly in individuals with high-grade and low-grade gliomas whose tumors are in locations that prevent full resection. Evidence from early-phase trials in individuals 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 individuals 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.

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 individuals with melanoma along with the concurrently approved diagnostic tests as of the most recent policy update (May 30, 2023).

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

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Table 1. FDA-Approved Targeted Treatments for Melanoma and Approved Companion Diagnostic Tests[1]

Treatment	Indication	FDA Approval of Companion Diagnostic Test	Pivotal Study	NCCN Recommendation Level/Guideline
Atezolizumab (Tecentriq®‡; Genentech)	• 2020: treatment of individuals with unresectable or metastatic melanoma with *BRAF* V600 variants in combination with cobimetinib and vemurafenib	For cobimetinib in combination with vemurafenib: • 2016: cobas®‡ 4800 BRAF V600 Mutation Test (Roche) • 2017: FoundationOne CDx™‡‡ (Foundation Medicine)	Gutzmer et al (2020)	2A or higher/ Cutaneous Melanoma (v.2.2023)
Binimetinib (Mektovi®‡; Array BioPharma)	• 2018: Used in combination with encorafenib to treat	• 2013: THxID™‡ BRAF kit	Dummer et al (2018)	2A or higher/ Cutaneous Melanoma (v.2.2023)

	individuals with unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation.	(bioMérieux)	Dummer et al (2022)	
Cobimetinib (Cotellic®‡; Genentech)	• 2015: Used in combination with vemurafenib to treat individuals 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)	Ascierto et al (2016)	2A or higher/ Cutaneous Melanoma (v.2.2023)
Dabrafenib (Tafinlar®‡; GlaxoSmithKline)	• 2013: treatment of individuals with unresectable or metastatic melanoma	Melanoma • 2013: THxID™‡ BRAF kit (bioMérieux)	Hauschild et al (2012) Long et al (2015)	2A or higher/ Cutaneous Melanoma (v.2.2023) Central Nervous

	with *BRAF* V600E • 2014: Used in combination with trametinib to treat individuals with unresectable or metastatic melanoma with *BRAF* V600E or V600K variants • 2018: Used in combination with trametinib for adjuvant treatment of individuals with resected stage III melanoma with *BRAF* V600E or V600K variants • 2023: Used in combination with trametinib for treatment of pediatric individuals 1 year of age and	• 2017: FoundationOne CDx™‡ (Foundation Medicine) Glioma • No companion FDA approved companion diagnostic	Long et al (2014) Robert et al (2015) Long et al (2017) Glioma: ClinicalTrials.gov (2023)	System Cancers (v.1.2023)

	older with low-grade glioma with a *BRAF* V600E mutation who require systemic therapy.			
Encorafenib (Bravtovi®‡; Array BioPharma)	• 2018: Used in combination with binimetinib to treat individuals with unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation	• 2013: THxID™‡ BRAF kit (bioMérieux)	Ascierto et al (2020)	2A or higher/ Cutaneous Melanoma (v.2.2023)
Entrectinib (Rozyltrek®‡; Genentech)	• 2019: treatment of adults and pediatric individuals 12 years of age and older with solid tumors that have a *NTRK* gene fusion without a known acquired	• No FDA-approved companion diagnostic		2A or higher/ Cutaneous Melanoma (v.2.2023)

	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			
Larotrectinib (Vitrakvi®‡; Loxo Oncology/Bayer)	• 2018: treatment of adult and pediatric individuals 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	• 2020: Foundation One CDx™‡ (Foundation Medicine)		2A or higher/ Cutaneous Melanoma (v.2.2023)

	morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment			
Pembrolizumab (Keytruda®‡; Merck)	• 2020: treatment of adult and pediatric individuals with unresectable or metastatic tumor mutation burden-high (TMB-H) [≥10 mutations/mega base] solid tumors, that have progressed following prior treatment and who have no satisfactory treatment options	• 2020: Foundation One CDx™‡ (Foundation Medicine)		2A or higher/ Cutaneous Melanoma (v.2.2023)

Vemurafenib (Zelboraf®)‡; Roche/Genentech and Plexxikon)	• 2011: treatment of individuals with unresectable or metastatic melanoma with *BRAF* V600 variants	• 2011: cobas®‡ 4800 BRAF V600 Mutation Test (Roche) • 2017: FoundationOne CDx™‡ (Foundation Medicine)	Chapman et al (2017)	2A or higher/ Cutaneous Melanoma (v.2.2023)
Trametinib (Mekinist™‡; GlaxoSmithKline)	• 2013: treatment of individuals with unresectable or metastatic melanoma with *BRAF* V600E or V600K variants • 2014: Used in combination with dabrafenib to treat individuals with unresectable or metastatic	• 2013: THxID™‡ BRAF kit (bioMérieux) • 2017: FoundationOne CDx™‡ (Foundation Medicine)	Flaherty et al (2012) Long et al (2015) Long et al (2014) Robert et al (2015) Long et al (2017)	2A or higher/ Cutaneous Melanoma (v.2.2023) Central Nervous System Cancers (v.1.2023)

	melanoma with *BRAF* V600E or V600K variants • 2018: Used in combination with dabrafenib for adjuvant treatment of individuals with resected stage III melanoma with *BRAF* V600E or V600K variants • 2023: Used in combination with dabrafenib for the treatment of pediatric individuals 1 year of age and older with low-grade glioma with a *BRAF* V600E mutation who require systemic therapy		Glioma: ClinicalTrials.gov (2023)	

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BRAF: b-raf proto-oncogene, serine/threonine kinase; FDA: Food and Drug Administration; NCCN: National Comprehensive Cancer Network; NTRK: Neurotrophic tyrosine receptor kinase; TMB: tumor mutational burden; TRK: tropomyosin receptor kinase.

[1] Please consult the FDA list of 'Cleared or Approved Companion Diagnostic Devices' for most current information.

FDA product code: OWD.

Laboratory-Developed Tests
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 (CLIA). Laboratories that offer laboratory-developed tests must be licensed under CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

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.

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 are drugs designed to target a somatic variant in the *BRAF* gene. *BRAF* and MEK inhibitors were originally developed for individuals 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.

Summary of Evidence
For individuals with melanoma who receive *BRAF* gene variant testing to select treatment with Food and Drug Administration (FDA)-approved targeted therapy, the evidence includes FDA-approved therapeutics with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

For individuals with glioma who receive *BRAF* gene variant testing to select treatment with FDA-approved targeted therapy, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

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
Note: Guidelines are updated frequently; refer to the source material for most recent guidelines.

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National Comprehensive Cancer Network (NCCN) guidelines for cutaneous melanoma (v.2.2023) include the following recommendations on somatic genetic testing relevant to this reference medical policy:

- The panel does not recommend *BRAF* or next generation sequencing (NGS) testing for resected stage I–II cutaneous melanoma unless it will inform clinical trial participation.
- BRAF mutation testing is recommended for individuals with stage III at high risk for recurrence for whom future *BRAF*-directed therapy may be an option.
- For initial presentation with stage IV disease or clinical recurrence, obtain tissue to ascertain alterations in *BRAF*, and in the appropriate clinical setting, KIT [receptor tyrosine kinase] from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy.
- Broader genomic profiling (e.g., larger NGS panels, *BRAF* non-V600 mutations) is recommended if feasible, especially if the test results might guide future treatment decisions or eligibility for participation in a clinical trial.
- 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).
- KIT mutations are present in 10%-15% of melanomas of mucosal (vulvovaginal, anorectal, sinonasal) and acral (palms, soles, nailbeds) origin. Thus, clinical features can guide the decision whether to perform KIT mutation testing.
- NRAS mutations appear to correlate with poor survival in localized and advanced melanoma. MEK inhibitors may produce responses in a minority of individuals with NRAS mutations. Given the low probability of overlapping targetable mutations (including BRAF and KIT mutations), the presence of an NRAS mutation may identify individuals who will not benefit from additional molecular testing.
- Existing and emerging GEP tests and other molecular techniques (i.e., circulating tumor DNA tests) should be prospectively compared to determine their clinical utility, including with no-cost, contemporary, multivariable SLNB risk prediction models.
- Repeat molecular testing upon recurrence or metastasis is likely to be of low yield, unless new or more comprehensive testing methods are used or a larger, more representative sample is available if there is concern for sampling error.

- Repeat testing following progression on targeted therapy (*BRAF*- or *KIT*-directed therapy) does not appear to have clinical utility, since the mechanisms of resistance are diverse and do not have prognostic or therapeutic relevance.

NCCN guidelines on central nervous system cancers (v.1.2023) include the following recommendation on somatic genetic testing in glioma relevant to this evidence review:

- The panel encourages molecular testing of glioblastoma because if a driver mutation (such as *BRAF* V600E mutation or NTRK fusion) 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.
- *IDH, ATRX, and TERT* promoter mutation testing is recommended for the workup of gliomas.
- *MGMT* promoter methylation is an essential part of molecular diagnostics for all high-grade gliomas (grade 3 and 4).
- *HD-3A, HIST1H3B, and BRAF* mutation testing is recommended in the appropriate clinical context.

NCCN guidelines on pediatric central nervous system cancers (v.2.2023) include a recommendation for testing of *BRAF* V600E mutation and *BRAF* fusion for pediatric gliomas, and further recommend that preferred systemic therapy options for recurrent disease include, but are not limited to, dabrafenib/trametinib or vemurafenib for *BRAF* V600E mutated tumors.

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 individuals 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 individuals 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.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
Melanoma			
NCT04722575	NEOadjuvant Plus Adjuvant Therapy With Combination or Sequence of Vemurafenib, cobimetinib, and atezolizumab in Individuals	88	Jun 2027

	With High-risk, Surgically Resectable BRAF Mutated and Wild-type Melanoma (NEO-TIM)		
NCT05768178	DETERMINE (Determining Extended Therapeutic Indications for Existing Drugs in Rare Molecularly Defined Indications Using a National Evaluation Platform Trial): An Umbrella-Basket Platform Trial to Evaluate the Efficacy of Targeted Therapies in Rare Adult, Pediatric and Teenage/Young Adult (TYA) Cancers With Actionable Genomic Alterations, Including Common Cancers With Rare Actionable Alterations Treatment Arm 5: Vemurafenib in Combination With Cobimetinib in Adult Individuals With BRAF Positive Cancers	30	Oct 2029
NCT05770544	DETERMINE (Determining Extended Therapeutic Indications for Existing Drugs in Rare Molecularly Defined Indications Using a National Evaluation Platform Trial): An Umbrella-Basket Platform Trial to Evaluate the Efficacy of Targeted Therapies in Rare Adult, Pediatric and Teenage/Young Adult (TYA) Cancers With Actionable Genomic Alterations, Including Common Cancers With Rare Actionable Alterations. Treatment Arm 3: Entrectinib in Adult, Teenage/Young Adults and Pediatric Individuals With ROS1 Gene Fusion-positive Cancers	30	Oct 2029
Glioma			

NCT01089101	A Phase 1 and Phase II and Re-Treatment Study of AZD6244 for Recurrent or Refractory Pediatric Low Grade Glioma	220	Dec 2025
NCT01748149[a]	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 *BRAF*V600E- or *BRAF* Ins T Mutant Brain Tumors	40	Dec 2023
NCT02285439	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	105	Feb 2024
NCT02465060	Molecular Analysis for Therapy Choice (MATCH)	6452	Dec 2025
NCT03220035	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice)- Phase 2 Subprotocol of Vemurafenib in Individuals With Tumors Harboring *BRAF* V600 Mutations	49	Jul 2023
NCT04166409	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)	220	Dec 2026
NCT03155620	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol	2316	Sep 2027

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

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Policy History

Original Effective Date: 11/16/2011
Current Effective Date: 10/09/2023

11/03/2011	Medical Policy Committee review
11/16/2011	Medical Policy Implementation Committee approval. New policy.
11/01/2012	Medical Policy Committee review
11/28/2012	Medical Policy Implementation Committee approval. "Targeted" added to the title. Eligible for coverage statement modified to read "FDA-approved BRAF inhibitors" in place of "vemurafenib" .
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.
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
09/07/2023	Medical Policy Committee review
09/13/2023	Medical Policy Implementation Committee approval. Added "or with resected stage III melanoma" as eligible for coverage. Deleted "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."
12/13/2023	Coding update

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 2022 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.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which 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.

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: 10/09/2023

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

Code Type	Code
CPT	0037U, 81191, 81192, 81193, 81194, 81210, 81287 Add codes effective 10/01/2023: 81120, 81121, 81345, 81479 Add codes effective 01/01/2024: 81457, 81458, 81459, 81462, 81463, 81464
HCPCS	No codes
ICD-10 Diagnosis	All related Diagnoses

*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 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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

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.