MEDICAL POLICY

POLICY TITLE	SOMATIC GENETIC TESTING TO SELECT INDIVIDUALS WITH MELANOMA OR GLIOMA FOR TARGETED THERAPY OR IMMUNOTHERAPY (BRAF)
POLICY NUMBER	MP 2.364

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**RETIRED 7/1/2026**

I. POLICY

Testing for *BRAF* V600 variants in individuals with unresectable or metastatic melanoma, or with resected stage III melanoma may be considered **medically necessary** to select individuals for treatment with Food and Drug Administration (FDA) approved BRAF inhibitors or MEK inhibitors (see Policy Guidelines).

Testing for *BRAF* V600 variants for all other individuals with melanoma is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Testing for *BRAF* V600E variants in individuals with glioma may be considered **medically necessary** to select individuals for targeted treatment with dabrafenib in combination with trametinib.

Testing for BRAF V600 variants for all other individuals with glioma to select targeted treatment is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Testing for NTRK gene fusions in individuals with unresectable or metastatic melanoma may be considered **medically necessary** to select individuals for treatment with FDA-approved kinase inhibitors (see Policy Guidelines).

Testing for NTRK gene fusions in individuals with glioma may be considered **medically necessary** to select individuals for treatment with FDA-approved kinase inhibitors.

Testing for NTRK gene fusions for all other individuals with melanoma or glioma to select targeted treatment other than FDA-approved kinase inhibitors is considered **investigational**.

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Policy Guidelines

If coverage of a test is requested, but is not listed above, please refer to **MP 2.259 - Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies** for additional guidance.

This policy does not address use of BRAF testing for the purpose of Central Nervous System (CNS) tumor diagnosis.

Testing for other variants may become available between policy updates.

Testing for individual genes (not gene panels) associated with FDA-approved therapeutics 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.

Cross-References:

MP 2.388 Somatic Biomarker Testing for Immune Checkpoint Inhibitor Therapy (MMI/MMR, PD-L1, TMB)
MP 2.241 - Molecular Analysis (Including Liquid Biopsy) for Targeted Therapy or Immunotherapy for Non-Small Cell Lung Cancer
MP 2.259 - Molecular Panel Testing of Cancers to Identify Targeted Therapies
MP 5.013 - Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
MP 2.316 Somatic Biomarker Testing for Targeted Treatment of Metastatic Colorectal Cancer

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital BlueCross and subject to benefit variations as discussed in Section VI. Please see additional information below.

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FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND

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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 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.

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 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 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.

Glioma

Gliomas encompass a heterogeneous group of tumors and 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).

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.

REGULATORY STATUS

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.

The FDA maintains a 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

Treatment	Indication	FDA Approval of Companion Diagnostic Test	NCCN Recommendation Level/ Guideline
Atezolizumab (Tecentriq®; Genentech)	2020: treatment of patients with unresectable or metastatic melanoma with *BRAF* V600	For cobimetinib in combination with vemurafenib:	2A or higher/

	variants in combination with cobimetinib and vemurafenib	2016: cobas® 4800 BRAF V600 Mutation Test (Roche) 2017: FoundationOne CDx™ (Foundation Medicine)	Cutaneous Melanoma (v.2.2024)
Binimetinib (Mektovi®; Array BioPharma)	2018: Used in combination with encorafenib to treat patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation	2013: THxID™ BRAF kit (bioMérieux)	2A or higher/ Cutaneous Melanoma (v.2.2024)
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)	2A or higher/ Cutaneous Melanoma (v.2.2024)
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 2023: Used in combination with trametinib for treatment of pediatric patients 1 year of age and older with low-grade glioma with a BRAF V600E mutation who require systemic therapy.	Melanoma: 2013: THxID™ BRAF kit (bioMérieux) 2017: FoundationOne CDx™ (Foundation Medicine) Glioma: No companion FDA approved companion diagnostic	2A or higher/ Cutaneous Melanoma (v.2.2024) Central Nervous System Cancers (v.1.2024)

Encorafenib (Bravtovi®; Array BioPharma)	2018: Used in combination with binimetinib to treat patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation	2013: THxID™ BRAF kit (bioMérieux)	2A or higher/ Cutaneous Melanoma (v.2.2024)
Entrectinib (Rozyltrek®; Genentech)	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 2023: Above indication expanded to pediatric patients older than 1 month of age	2022: FoundationOne CDx (Foundation Medicine) 2022: FoundationOne Liquid CDx (Foundation Medicine)	2A or higher/ Cutaneous Melanoma (v.2.2024) Central Nervous System Cancers (v.1.2023) Pediatric CNS Cancers (v.1.2024)
Larotrectinib (Vitrakvi®; Loxo Oncology/Bayer)	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	2020: FoundationOne CDx™ (Foundation Medicine)	2A or higher/ Cutaneous Melanoma (v.2.2024) Central Nervous System Cancers (v.1.2023) Pediatric CNS Cancers (v.1.2024
Pembrolizumab (Keytruda®; Merck)	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	2020: FoundationOne CDx™ (Foundation Medicine)	2A or higher/ Cutaneous Melanoma (v.2.2024)
Vemurafenib (Zelboraf®); Roche/	2011: treatment of patients with unresectable or metastatic	2011: cobas® 4800 BRAF V600	2A or higher/

Genentech and Plexxikon)	melanoma with BRAF V600 variants	Mutation Test (Roche) 2017: FoundationOne CDx™ (Foundation Medicine)	Cutaneous Melanoma (v.2.2024)
Trametinib (Mekinist™; GlaxoSmithKline)	2013: treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K variants 2014: Used in combination with dabrafenib to treat patients with unresectable or metastatic melanoma with BRAF V600E or V600K variants 2018: Used in combination with dabrafenib for adjuvant treatment of patients with resected stage III melanoma with BRAF V600E or V600K variants 2023: Used in combination with dabrafenib for the treatment of pediatric patients 1 year of age and older with low-grade glioma with a BRAF V600E mutation who require systemic therapy	2013: THxID™ BRAF kit (bioMérieux) 2017: FoundationOne CDx™ (Foundation Medicine)	2A or higher/ Cutaneous Melanoma (v.2.2024) Central Nervous System Cancers (v.1.2023)

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.
FDA product code: OWD

IV. RATIONALE

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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.

For individuals with melanoma who receive NTRK gene fusion 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 NTRK gene fusion 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.

V. DEFINITIONS

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NA

VI. DISCLAIMER

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Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These polices are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

VII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

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Procedure Codes								
0473U	81191	81192	81193	81194	81210			

Investigational: therefore, not covered when used for tumor mutational burden (TMB):

Procedure Codes								
0037U								

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ICD-10-CM Diagnosis Code	Description
C43.0	Malignant melanoma of lip
C43.10	Malignant melanoma of unspecified eyelid, including canthus
C43.111	Malignant melanoma of right upper eyelid, including canthus
C43.112	Malignant melanoma of right lower eyelid, including canthus
C43.121	Malignant melanoma of left upper eyelid, including canthus
C43.122	Malignant melanoma of left lower eyelid, including canthus
C43.20	Malignant melanoma of unspecified ear and external auricular canal
C43.21	Malignant melanoma of right ear and external auricular canal
C43.22	Malignant melanoma of left ear and external auricular canal
C43.30	Malignant melanoma of unspecified part of face
C43.31	Malignant melanoma of nose
C43.39	Malignant melanoma of other parts of face
C43.4	Malignant melanoma of scalp and neck
C43.51	Malignant melanoma of anal skin (includes margin and perianal skin)
C43.52	Malignant melanoma of skin of breast
C43.59	Malignant melanoma of other part of trunk
C43.60	Malignant melanoma of unspecified upper limb, including shoulder
C43.61	Malignant melanoma of right upper limb, including shoulder
C43.62	Malignant melanoma of left upper limb, including shoulder
C43.70	Malignant melanoma of unspecified lower limb, including hip
C43.71	Malignant melanoma of right lower limb, including hip
C43.72	Malignant melanoma of left lower limb, including hip
C43.8	Malignant melanoma of overlapping sites of skin
C43.9	Malignant melanoma of skin, unspecified
C71.0	Malignant neoplasm of cerebrum, except lobes and ventricles
C71.1	Malignant neoplasm of frontal lobe
C71.2	Malignant neoplasm of temporal lobe
C71.3	Malignant neoplasm of parietal lobe
C71.4	Malignant neoplasm of occipital lobe
C71.5	Malignant neoplasm of cerebral ventricle
C71.6	Malignant neoplasm of cerebellum
C71.7	Malignant neoplasm of brain stem
C71.8	Malignant neoplasm of overlapping sites of brain
C71.9	Malignant neoplasm of brain, unspecified

VIII. REFERENCES

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IX. POLICY HISTORY

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MP 2.364	**09/10/2020 Consensus Review.** No change to policy statements. Added code C43.112. References updated. Description/Background section revised.
	05/20/2021 Consensus Review. Policy statement unchanged. Background, Rationale and References updated
	09/29/2022 Minor Review. Title changed from "BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy" to "Somatic Genetic Testing to Select Individuals with Melanoma or Glioma for Targeted Therapy or Immunotherapy". Added immunotherapy as medically necessary for BRAF V600 variant testing with unresectable or metastatic melanoma. Added statement "Testing for tumor mutational burden (TMB) in individuals with unresectable or metastatic melanoma or glioma to select individuals for treatment with FDA-approved immunotherapy is considered investigational. Testing for other variants may become available between policy updates." Policy Guidelines updated. NCCN language and additional cross-referenced policies added. FEP language revised. Background, Rationale and References updated. Added code 0037U as investigational.
	11/07/2023 Minor Review. Testing for BRAF V600 variants for glioma changed from investigational to medically necessary for BRAF V600E variants to individuals for targeted treatment with dabrafenib in combination with trametinib. Tumor Mutational Burden criteria removed and placed on MP 2.388. Policy Guideline updated with addition of referenced MP 2.259 if test is requested but not listed in policy. Statement that testing for other variants may become available between policy updates moved from policy statement section to policy guidelines section. Cross referenced MP 2.388 Somatic Biomarker Testing for Immune Checkpoint Inhibitor Therapy (MMI/MMR, PD-L1, TMB) added. Background and Rationale updated. ICD10 codes C71.0 - C71.9 added. References revised.
	04/11/2024 Administrative Update. Indications related to immunotherapy removed and placed into MP 2.388 Somatic Biomarker Testing For Immune Checkpoint Inhibitor Therapy (MSIMMR, PD-L1, TMB). CPT 81210 removed and moved to MP 2.388. No change to policy statements. Effective 05/01/2024.
	06/12/2024 Administrative Update. New code 0473U added; effective 07/01/2024.
	11/19/2024 Minor Review. Added criteria for NTRK gene fusion testing to select targeted treatment. Statement on BRAF V600 variant testing in cutaneous melanoma revised to include either tissue or liquid biopsy. Policy Guidelines revised. Cross Referenced policies, Background and Rationale updated. Added codes 81191, 81192, 81193, 81194. References added.

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	06/12/2025 Administrative Update. Removed Benefit Variations Section and updated Disclaimer.
	01/23/2026 Retirement Review.

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