BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.77 Somatic Genetic Testing to Select Individuals with Melanoma or Glioma for Targeted Therapy (BRAF)

Effective Policy Date: October 1, 2023

Original Policy Date: April 2012

Related Policies:

2.04.08 - Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
2.04.115 - Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies
2.04.157 - Somatic Biomarker Testing for Immune Checkpoint Inhibitor Therapy (BRAF, MSI/MMR, PD-L1, TMB)
2.04.45 - Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Non-Small-Cell Lung Cancer (EGFR, ALK, BRAF, ROS1, RET, MET, KRAS, HER2, PD-L1, TMB)

Somatic Genetic Testing to Select Individuals with Melanoma or Glioma for Targeted Therapy (BRAF)

Description

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 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.

OBJECTIVE

The objective of this review is to summarize the evidence and guidelines on testing for *BRAF* variants to select treatment with FDA-approved targeted therapy for individuals with melanoma or glioma.

POLICY STATEMENT

Testing for *BRAF* V600 variants in tumor tissue of individuals with unresectable or metastatic melanoma, or with resected stage III melanoma may be considered **medically necessary** to select individuals for treatment with FDA-approved BRAF inhibitors or MEK inhibitors.

Testing for *BRAF* V600 variants for all other individuals with melanoma is considered **investigational**.

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**.

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.

The use of tropomyosin receptor kinase (TRK) inhibitors for individuals with neurotrophic tyrosine receptor kinase (NTRK*)* gene fusion-positive solid tumors is addressed separately in evidence review 5.01.31.

For expanded panel testing, see evidence review 2.04.115.

For somatic biomarker testing related to use of immune checkpoint inhibitor therapy (*BRAF,* microsatellite instability/mismatch repair [MSI/MMR], PD-L1, tumor mutational burden [TMB]), see evidence review 2.04.157.

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.

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 regardless of NCCN recommendations, as these off-label therapies are deemed investigational per the Blue Cross and Blue Shield Association Medical Policy Program Policies and Procedures.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA 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 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.[9,]

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 patients 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)[10,]	2A or higher/ Cutaneous Melanoma (v.2.2023)[11,]
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 (bioMrieux)	Dummer et al (2018)[12,] Dummer et al (2022)[13,]	2A or higher/ Cutaneous Melanoma (v.2.2023)[11,]
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)	Ascierto et al (2016)[14,]	2A or higher/ Cutaneous Melanoma (v.2.2023)[11,]
Dabrafenib (Tafinlar; GlaxoSmithKline)	• 2013: treatment of patients with unresectable or	Melanoma	Hauschild et al (2012)[15,] Long et al (2015)[16,]	2A or higher/ Cutaneous

	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.	• 2013: THxID™ BRAF kit (bioMrieux) • 2017: FoundationOne CDx™ (Foundation Medicine) Glioma • No companion FDA approved companion diagnostic	Long et al (2014)[17], Robert et al (2015)[18], Long et al (2017)[19], Glioma: ClinicalTrials.gov (2023)[20],	Melanoma (v.2.2023)[11], Central Nervous System Cancers (v.1.2023)[21],
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 (bioMrieux)	Ascierto et al (2020)[22],	2A or higher/ Cutaneous Melanoma (v.2.2023)[11],
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	• No FDA-approved companion diagnostic	See evidence review 5.01.31	2A or higher/ Cutaneous Melanoma (v.2.2023)[11],
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)	See evidence review 5.01.31	2A or higher/ Cutaneous Melanoma (v.2.2023)[11],

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)	See evidence review 2.04.157	2A or higher/ Cutaneous Melanoma (v.2.2023)[11],
Vemurafenib (Zelboraf); Roche/Genentech and Plexxikon)	• 2011: treatment of patients with unresectable or metastatic melanoma with *BRAF* V600 variants	• 2011: cobas 4800 BRAF V600 Mutation Test (Roche) • 2017: FoundationOne CDx™ (Foundation Medicine)	Chapman et al (2017)[23],	2A or higher/ Cutaneous Melanoma (v.2.2023)[11],
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 (bioMrieux) • 2017: FoundationOne CDx™ (Foundation Medicine)	Flaherty et al (2012)[24], Long et al (2015)[16], Long et al (2014)[17], Robert et al (2015)[18], Long et al (2017)[19], Glioma: ClinicalTrials.gov (2023)[20],	2A or higher/ Cutaneous Melanoma (v.2.2023)[11], Central Nervous System Cancers (v.1.2023)[21],

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.[9],

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

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

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.

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:[11,]

- 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 patients 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).

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:[21,]

- 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.

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.[25,]

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:[26,]

1. Patient has:
    1. either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and
    2. not been previously tested with the same test using NGS for the same cancer genetic content, and
    3. decided to seek further cancer treatment (eg, therapeutic chemotherapy).
2. The diagnostic laboratory test using NGS must have:
    1. Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,
    2. an FDA-approved or -cleared indication for use in that patient"s cancer; and,
    3. 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.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
March 2012	New policy	
December 2012	Replace policy	Policy and references updated with literature review, Policy statement modified to read "FDA-approved BRAF inhibitors, in place of "vemurafenib,. Added to Policy guidelines: "Currently only vemurefenib has FDA approval for treatment of advanced melanoma
December 2013	Replace policy	Policy updated with literature review through August 2013, references 10-12, 14-15, 23-26, and 29 added; references 1, 13, and 30 updated. Policy statements modified to read, "Testing for BRAFV600 mutations, in place of "Testing for the BRAFV600 mutation.,
December 2014	Replace policy	Policy updated with literature review through September 2, 2014, references were updated, and none were added. Policy statements were revised to align with current FDA approved indication, i.e., "unresectable or metastatic, rather than stage IIC or IV.,
September 2017	Replace policy	Policy updated with literature review through April 25, 2017; references 3-7,19-31, 43-45, 50-51, and 53-65 added. Policy revised with updated genetics nomenclature. Information about additional FDA-approved BRAF inhibitor (nivolumab) added to policy. 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,
September 2018	Replace policy	Policy updated with literature review through April 9, 2018; references 36, 38, 41, 44, 50 and 51 added. Policy statements on BRAF testing in unresectable, metastatic melanoma and in glioma unchanged. New policy statement added stating BRAF testing in resected, stage III melanoma is medically necessary. "Mutation, changed to "variant, in policy title.
September 2019	Replace policy	Policy updated with literature review through April 18, 2019; references added. Policy statements unchanged.
September 2020	Replace policy	Policy updated with literature review through April 21, 2020; references added. Policy statements unchanged.
September 2021	Replace policy	Policy updated with literature review through May 7, 2021; references added. 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."
September 2022	Replace policy	Policy updated with literature review through May 9, 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.
September 2023	Replace policy	Policy updated with literature review through May 11, 2023. Policy extensively pruned. Pivotal studies added to Table 1. Policy statements changed to align with PICO. New policy statement added stating BRAF V600E variants in individuals with glioma may be considered medically necessary to select individuals for targeted treatment with dabrafenib in combination with trametinib. Indications related to immunotherapy and tumor mutational burden testing removed and added to new policy 2.04.157.