Medical Policy

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***Current Policy Effective Date: 1/1/26**
(See policy history boxes for previous effective dates)

Title: Genetic Testing—BRAF/NTRK Mutation in Selecting Melanoma Patients for Targeted Therapy Including Liquid Biopsy

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.

The neurotrophic receptor tyrosine 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 is a kinase inhibitor of TRK A, B, and C protein. Entrectinib additionally inhibits 2 other kinases: anaplastic lymphoma kinase and proto-oncogene tyrosine-protein kinase. The presence of *NTRK* gene fusions can be detected by multiple methods including next-generation sequencing, reverse transcription-polymerase chain reaction, fluorescence in situ hybridization and immunohistochemistry.

Medical Policy Statement

Testing for *BRAF* V600 variants (in tissue or blood) in individuals with unresectable or metastatic melanoma or with resected stage III melanoma is established when criteria are met.

Molecular testing for NTRK gene fusions (in tissue or blood) in individuals with unresectable or metastatic melanoma is established when criteria are met.

Molecular testing on peripheral blood (i.e., liquid biopsy, ctDNA) is established when criteria are met.

Inclusionary and Exclusionary Guidelines

Please refer to the pharmacy Genetic Testing of Drugs policy (Atezolizumab, Binimetinib, Dabrafenib, Encorafenib, Entrectinib, Larotrectinib, Pembrolizumab, Vemurafenib, Trametinib, and Cobimetinib) for patient selection.

Circulating Tumor DNA (liquid biopsy)
The clinical utility of circulating tumor DNA and circulating tumor cells for management of advanced solid cancers has been established when **ALL** of the following criteria are met.

- May be considered established for guidance in the selection of appropriate targeted FDA therapeutic options for **ANY** of the following conditions:
    - Metastatic cancers
    - Inoperable locally advanced cancers
    - Refractory cancers
    - Recurrent cancers
    - Advanced cancer (stages III or IV); **AND**
- Individuals have not been previously tested using the same liquid biopsy panel, unless a new primary cancer diagnosis is made, and further cancer treatment is being considered **OR** individual is experiencing a relapse; **AND**
- There is clinical documentation that tissue-based testing cannot be performed (e.g., insufficient sample, inaccessible tumor or where there may be a delay in obtaining tumor sample) **OR** tissue-based testing is not required when there is an FDA-approved companion diagnostic device that is a circulating tumor test (liquid biopsy panel).

U.S. Food & Drug Administration – Companion Diagnostics
A companion diagnostic is an FDA approved medical device, often an in vitro device, which provides information that is essential for the safe and effective use of a corresponding drug or biological product.(2) The test helps a health care professional determine whether, for a specific patient, a particular therapeutic product's benefits outweigh any potential serious side effects or risks.

Companion diagnostics can:
- identify patients who are most likely to benefit from a particular therapeutic product;

- identify patients likely to be at increased risk for serious side effects as a result of treatment with a particular therapeutic product; or
- monitor response to treatment with a particular therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness.

FDA-Approved Companion Diagnostic Tests
FDA-approved companion diagnostic tests include:
- Tests which are billed with CPT* codes (most laboratories are able to process these)
- Proprietary laboratory analyses (PLA) tests (processed by one specific independent laboratory). Most PLA tests have billing codes that end in "U."

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Proprietary Laboratory Analyses (PLA) Testing
A PLA test is considered **established** when the following criteria are met:
- Biomarker confirmation is required by an FDA-approved or -cleared test prior to initiating treatment (as described in the FDA prescribing label of the therapeutic in the section "Indications and Usage"), **AND**
- The test is an FDA-approved companion diagnostic.

Information regarding FDA-approved companion diagnostic tests should be obtained from the FDA "List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)" website. www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools

For accuracy, the reader is advised to access the information directly from the FDA site. (This website is updated frequently)

Exclusions:
- The use of circulating tumor DNA and circulating tumor cells is considered investigational when criteria above are not met.
- The use of circulating tumor DNA and circulating tumor cell testing is considered investigational for all other indications related to solid tumors, including measurable residual disease (MRD) testing and cancer screening (e.g., Galleri).
- Testing for BRAF V600 variants for all other melanoma diagnoses.
- Testing for NTRK variants for all other melanoma diagnoses.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81191	81192	81193	81194	81210	81445	81455	81456	0037U*	0211U
0239U*	0242U*	0326U*							

*Test is covered when tissue biopsy is not available

Other codes (investigational, not medically necessary, etc.):

N/A

Background

MELANOMA

Overall incidence rates for melanoma have been increasing for at least 30 years.[1] 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 *BRAF* kinase gene are common in tumors of patients with advanced melanoma and result in constitutive activation of a key signaling pathway (*RAF-MEK-ERK* pathway) that is associated with oncogenic proliferation. In general, 50% to 70% of melanoma tumors harbor a *BRAF* variant; of these, 80% are positive for the *BRAF* V600E variant, and 16% are positive for *BRAF* V600K.[1] Thus, 45% to 60% of advanced melanoma patients may respond to a *BRAF* inhibitor targeted to this mutated kinase.

BRAF inhibitors (vemurafenib, dabrafenib) and MEK inhibitors (trametinib, cobimetinib) have been developed for 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.[2] Preclinical studies have demonstrated that vemurafenib selectively blocked the RAF-MEK-ERK pathway in *BRAF* mutant cells[3-5] 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,[3-5] 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 receptor tyrosine kinase *(NTRK)* gene fusions are uncommon kinase fusion events that drive tumorigenesis in a small fraction of solid tumors, regardless of tissue type.[6,] 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 1,500-5,000 cases in the United States.[7] *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.[8]

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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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Rationale

Evidence reviews assess clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to individuals and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms. The following is a summary of the key literature to date.

Clinical Context and Test Purpose

The purpose of testing for *BRAF* pathogenic variants in individuals with unresectable or metastatic melanoma is to inform a decision whether to treat with BRAF and/or MEK tyrosine kinase inhibitors, alone or in combination with immunotherapy, or with other standard treatments for metastatic melanoma. At the time of the early trials of targeted therapy for metastatic melanoma, cytotoxic chemotherapy (e.g., dacarbazine, temozolomide) was widely used to treat metastatic melanoma and was therefore considered a comparator, although it was never demonstrated to improve survival. Chemotherapy is now generally used only in second- or third-line settings or not at all. The current standard treatment for patients with metastatic melanoma includes immunotherapy, which is effective in patients with and without *BRAF* V600 variants. Patients whose tumors contain a *BRAF* V600 pathogenic variant may receive a BRAF inhibitor and/or a MEK inhibitor instead of or following immunotherapy.

Unresectable or Metastatic Melanoma

For several decades after its approval in 1975, cytotoxic chemotherapy with dacarbazine was considered the standard systemic therapy but has provided disappointingly low response rates

of only 15% to 25% and median response duration of 5 to 6 months; less than 5% of responses are complete.[2] Temozolomide has similar efficacy and, unlike dacarbazine, has much better efficacy with central nervous system tumors. Recently immunotherapy with ipilimumab or with checkpoint inhibitors such as pembrolizumab and nivolumab has demonstrated superior efficacy to chemotherapy[10,11,12,13,14] regardless of BRAF status and is now recommended as a potential first-line treatment of metastatic or unresectable melanoma.

Resected Stage III Melanoma

Wide local excision is the definitive surgical treatment of melanoma. Following surgery, patients with American Joint Committee on Cancer stage III melanoma may receive adjuvant therapy. Ipilimumab, a monoclonal antibody targeting cytotoxic T-lymphocyte antigen 4, has been shown to prolong recurrence-free survival by approximately 25% compared with placebo at a median of 5.3 years in patients who had resected stage III disease.[15] Nivolumab, a programmed cell death protein 1 blocking antibody has been shown to further prolong survival compared with ipilimumab by approximately 35% at 18 months.[16] Before the development of checkpoint inhibitor immunotherapy and targeted therapy, high-dose interferon alfa was an option for adjuvant treatment of stage III melanoma. Interferon alfa has demonstrated an improvement in overall survival but with numerous serious side effects.[17]

Clinically Valid and Clinically Useful

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Review of Evidence

Vemurafenib

The primary evidence of clinical validity and utility for BRAF variant testing is provided by the phase 3 clinical trial of vemurafenib that enrolled patients testing positive for a V600 variant as detected by the cobas 4800 *BRAF* V600 mutation test.

The BRIM-3 trial as reported by Chapman et al (2011) randomized 675 patients to vemurafenib (960 mg twice daily orally) or to dacarbazine (1000 mg/m^2 body surface area by intravenous infusion every 3 weeks) to determine whether vemurafenib would prolong the rate of OS or PFS compared with dacarbazine.[18] All enrolled patients had unresectable, previously untreated stage IIIC or IV melanoma with no active central nervous system metastases. Melanoma specimens from all patients tested positive for the *BRAF* V600E variant on the cobas 4800 BRAF V600 Mutation Test. Included were 19 patients with *BRAF* V600K variants and 1 with a *BRAF* V600D variant.

Primary endpoints were the rate of OS and PFS. An interim analysis was planned at 98 deaths and a final analysis at 196 deaths; the published report is the interim analysis. The data and safety monitoring board determined that both coprimary endpoints had met prespecified stopping criteria and recommended that patients in the dacarbazine group be allowed to cross over to receive vemurafenib. At the time the trial was halted, 118 patients had died; median survival had not been reached. Results for OS strongly favored vemurafenib, with a hazard ratio (HR) of 0.37 (95% confidence interval[CI], 0.26 to 0.55). Adverse events in the vemurafenib group included grade 2 or 3 photosensitivity skin reactions in 12% of patients and

cutaneous squamous cell carcinoma in 18%. The results of this trial comprised the efficacy and safety data supporting vemurafenib submission to the FDA and established safety and effectiveness of the cobas 4800 BRAF V600 Mutation Test, resulting in approval of both the drug and companion test.

Final OS results from BRIM-3 were reported by Chapman et al (2017).[19] Eighty-four (25%) of the 338 dacarbazine patients crossed over to vemurafenib and overall, 173 (51%) of the 338 patients in the dacarbazine group and 175 of the 337 patients (52%) in the vemurafenib group received subsequent anticancer therapies, most commonly ipilimumab. Median OS without censoring at crossover was 13.6 months (95% CI, 12.0 to 15.4) in vemurafenib vs. 10.3 months (95% CI, 9.1 to 12.8 months) in dacarbazine (HR=0.81; 95% CI, 0.68 to 0.96); p=0.01).

Table 1. Phase 3 RCTs of BRAF and MEK Inhibitors for BRAF-Positive Advanced Melanoma

Study/Year	FU, mo	Group	N	OS (95% CI)	PFS (95% CI), mo	ORR (95% CI)
Vemurafenib						
Chapman et al (2011)[18]	6	Vemurafenib	337	84 (78 to 89)	5.3[a]	48 (42 to 55)
		Dacarbazine	338	65 (56 to 73)	1.6[a]	5 (3 to 9)
		Hazard ratio		0.37 (0.26 to 0.55)	0.26 (0.20 to 0.33)	NA
		p		<0.001	<0.001	NA
Dabrafenib						
Hauschild et al (2012)[20]	4.9[a] 0-9.9[b]	Dabrafenib	187	89	5.1[a]	50 (42.4 to 57.1)
		Dacarbazine	63	86	2.7[a]	6 (1.8 to 15.5)
		Hazard ratio		0.61 (0.25 to 1.48)	0.33 (0.20 to 0.54)	NA
		p		NR	<0.001	NA
Trametinib						
Flaherty et al (2012)[21]	6	Trametinib	214	81	4.8[a]	22 (17 to 28)
		Chemotherapy[c]	108	67	1.5[a]	8 (4 to 15)
		Hazard ratio		0.54 (0.32 to 0.92)	0.47 (0.34 to 0.65)	NA
		p		0.01	<0.001	NA
Dabrafenib + Trametinib						
Long et al (2015)[22]		Dabrafenib + Trametinib	211	74	11.0	NA
		Dabrafenib	212	68	8.8	NA
		Hazard ratio		0.71 (0.55 to 0.92)	0.67 (0.53 to 0.84)	NA
		p		0.01	<0.001	0.001
Robert et al (2015)[23]	NR	Dabrafenib + Trametinib	352	72	11.4	64
		Vemurafenib	352	65	7.3	51
		Hazard ratio		0.69 (0.53 to 0.89)	0.56 (0.46 to 0.69)	NA
		P		0.005	0.001	0.001
Vemurafenib + Cobimetinib						
Ascierto et al (2016)[24]	14[a]	Vemurafenib + Cobimetinib	248	22.3 (20.3 to NE)	12.3 (9.5 to 13.4)	68 (61 to 73)
		Vemurafenib	247	17.4 (15.0 to 19.8)	7.2 (5.6 to 7.5)	45 (38 to 51)
		Hazard ratio		0.70 (0.55 to 0.90)	0.58 (0.46 to 0.72)	NA

		p		0.005	<0.001	<0.001
Encorafenib + Binimetinib						
Dummer et al (2018)[25]	17[a]	Encorafenib + Binimetinib	192	NR	14.9 (11.0 to 18.5)	63 (56 to 70)
		Encorafenib	194	NR	9.6 (7.5 to 14.8)	51 (43 to 58)
		Vemurafenib	191		7.3 (5.6 to 8.2)	40 (33 to 48)
		Hazard ratio[d]			0.54 (0.41 to 0.71)	NR
		p			<0.001	
Ascierto et al (2020)[30,]	48.8[a]	Encorafenib plus binimetinib	192	47% (NR) 33.6 (24.4 to 39.2)[a]	14.9 (11.0 to 20.2)[a]	64% (56% to 70%)
		Encorafenib	194	41% (NR) 23.5 (19.6 to 33.6)[a]	9.6 (7.4 to 14.8)[a]	52% (44% to 59%)
		Vemurafenib	191	31% (NR) 16.9 (14.0 to 24.5)[a]	7.3 (5.6 to 7.9)[a]	41% (34% to 48%)
		Hazard ratio[d]		0.61 (0.48 to 0.79)	0.51 (0.39 to 0.67)	NR
		p		NR	NR	NR
Atezolizumab plus vemurafenib and cobimetinib						
Gutzmer et al (2020)[31,]	18.9[a]	Atezolizumab plus vemurafenib and cobimetinib	256	64% (NR)	15.1 (11.4 to 18.4)[a]	66.3% (60.1% to 72.1%)
		Placebo plus vemurafenib and cobimetinib	258	57% (NR)	10.6 (9.3 to 12.7)[a]	65.0% (58.7% to 71.0%)
		Hazard ratio		0.85 (0.64 to 1.11)	0.78 (0.63 to 0.97)	NR
		p		23	.0249	NR

CI: confidence interval; FU: follow-up; NA: not applicable; NE: not estimable; NR: not reported; ORR: objective response rate (including complete and partial responses); OS: overall survival; PFS: progression-free survival; RCT: randomized controlled trial.
[a] Median value.
[b] Range.
[c] Either intravenous dacarbazine 1000 mg/m^2 or intravenous paclitaxel 175 mg/m^2 every 3 weeks at investigator discretion.
[d] Compared encorafenib plus binimetinib with vemurafenib.

Dabrafenib

One phase 3, open-label RCT of dabrafenib for advanced (stage IV or unresectable stage III) melanoma has been published[20]; the results of this trial are summarized in Table 2. The main objective of this RCT was to compare the efficacy of dabrafenib with standard dacarbazine treatment in patients who had *BRAF* V600E−variant metastatic melanoma. Two hundred fifty patients were randomized 3:1 to oral dabrafenib 150 mg twice daily or to intravenous dacarbazine 1000 mg/m2 every 3 weeks. The primary outcome was PFS, and secondary outcomes were OS, objective response rate, and adverse events.

Median PFS for the dabrafenib and dacarbazine groups was 5.1 months and 2.7 months (p<0.001), respectively. The OS did not differ significantly between groups: 11% of patients in the dabrafenib group died compared with 14% in the dacarbazine group (HR=0.61; 95% CI, 0.25 to 1.48). However, 28 (44%) patients in the dacarbazine arm crossed over at disease progression to receive dabrafenib. The objective response rate, defined as complete plus partial responses, was higher in the dabrafenib group (50%; 95% CI, 42.4% to 57.1%) than in the dacarbazine group (6%; 95% CI, 1.8% to 15.5%). Treatment-related adverse events of

grade 2 or higher occurred in 53% of patients who received dabrafenib and in 44% of patients who received dacarbazine. Grade 3 and 4 adverse events were uncommon in both groups. The most common serious adverse events were cutaneous squamous cell carcinoma (7% vs. none in controls); serious noninfectious, febrile drug reactions (3% grade 3 pyrexia vs. none in controls); and severe hyperglycemia (>250-500 mg/dL) requiring medical management in nondiabetic patients or change in management of diabetic patients (6% vs. none in controls).

Trametinib

The clinical efficacy and safety of trametinib were assessed in the phase 3, open-label METRIC trial.[21] Patients with stage IV or unresectable stage IIIC cutaneous melanoma were randomized 2:1 to trametinib 2 mg orally once daily (n=214) or to chemotherapy (n=108), either dacarbazine 1000 mg/m^2 intravenously every 3 weeks or paclitaxel 175 mg/m^2 intravenously every 3 weeks at investigator discretion. Most patients (67%) were previously untreated. The primary efficacy endpoint was PFS; secondary endpoints included OS, overall response rate, and safety. Tumor assessments were performed at baseline and weeks 6, 12, 21, and 30 and then every 12 weeks.

Median PFS was 4.8 months (95% CI, 4.3 to 4.9 months) in the trametinib arm and 1.5 months (95% CI, 1.4 to 2.7 months) in the chemotherapy arm (p<0.001) (see Table 2). Although median OS had not been reached at the time of the report publication, 6-month survival was statistically longer in the trametinib group than in the chemotherapy group (p=0.01); 51 (47%) of 108 patients in the chemotherapy group had crossed over at disease progression to receive trametinib. Decreased ejection fraction or ventricular dysfunction was observed in 14 (7%) patients in the trametinib group; 2 patients had grade 3 cardiac events that led to permanent drug discontinuation. Twelve percent of the trametinib group and 3% of the chemotherapy group experienced grade 3 hypertension. Nine percent of patients in the trametinib group experienced ocular events (mostly grade 1 or 2), most commonly blurred vision (4%). The most common adverse events in the trametinib group were rash, diarrhea, peripheral edema, and fatigue; rash was grade 3 or 4 in 16 (8%) patients. Cutaneous squamous cell carcinoma was not observed during treatment.

Combination *BRAF* Plus *MEK* Inhibitors

Dabrafenib and Trametinib

The efficacy of combination dabrafenib plus trametinib treatment has been established with two, phase 3 clinical trials.[23,22,26] This combination agent was evaluated in the phase 3 open-label trial by Long et al (2014, 2015).[22,26] In this trial, 4234 patients with unresectable stage IIC or stage IV melanoma with a *BRAF* V600E or V600K variant were randomized to dabrafenib plus trametinib or dabrafenib plus placebo. The primary endpoint was PFS, as reported in the first publication,[46] followed by a second publication in which longer-term OS was reported.[22]

Median PFS was 11.0 months in the dabrafenib plus trametinib group and 8.8 months in the dabrafenib-only group. The overall response rate was 67% in the dabrafenib plus trametinib group and 51% in the dabrafenib-only group. An interim OS analysis showed a statistically significant difference using standard statistical criteria, but the difference did not cross the prespecified stopping boundary. The rate of cutaneous squamous cell carcinoma was lower in the dabrafenib plus trametinib group (2% vs. 9%), whereas pyrexia occurred in more patients (51% vs. 28%). In the longer-term study assessing OS, median survival was 25.1 months in the dabrafenib plus trametinib group and 18.7 months in the dabrafenib-only group.

Another phase 3 RCT, by Roberts et al (2015), compared dabrafenib plus trametinib with vemurafenib.[23] A total of 704 patients with metastatic melanoma with *BRAF* V600E or V600K variants were randomized equally. The trial was terminated at a preplanned interim OS analysis. The OS rate at 12 months was 72% for dabrafenib plus trametinib and 65% for vemurafenib (p=0.005) (see Table 2). Median PFS was 11.4 months for dabrafenib plus trametinib and 7.3 months for vemurafenib (p<0.001). The objective response rate was 64% for dabrafenib plus trametinib and 51% for vemurafenib (p<0.001). Rates of severe adverse events were similar in both groups. Cutaneous squamous cell carcinoma and keratoacanthoma occurred in 1% of dabrafenib plus trametinib subjects and 18% of vemurafenib subjects.

Vemurafenib and Cobimetinib

A multicenter, randomized, double-blinded, placebo-controlled phase 3 trial evaluated vemurafenib plus cobimetinib in 495 patients with previously untreated, *BRAF* V600 variant−positive, unresectable or metastatic melanoma.[24] All patients received vemurafenib 960 mg orally twice daily on days 1 to 28 and were randomized 1:1 to also receive cobimetinib 60 mg once daily on days 1 to 21 or to placebo. The primary outcome was PFS. Analyses were done on the intention-to-treat population. Median follow-up was 14 months (see Table 2). PFS was significantly increased with vemurafenib plus cobimetinib compared with vemurafenib plus placebo (median PFS, 12.3 months vs. 7.2 months; HR=0.58; 95% CI, 0.46 to 0.72; p<0.001). Median OS was 22 months for vemurafenib plus cobimetinib and 17 months for vemurafenib plus placebo (HR=0.70; 95% CI, 0.55 to 0.90; p=0.005). Serious adverse events were reported in 92 (37%) patients in the vemurafenib plus cobimetinib group and 69 (28%) patients in the vemurafenib plus placebo group. The most common serious adverse events in the vemurafenib plus cobimetinib group were pyrexia and dehydration. The most common grade 3 or 4 adverse events occurring in the vemurafenib plus cobimetinib group were γ-glutamyl transferase increase, blood creatine phosphokinase increase, and alanine transaminase.

Encorafenib and Binimetinib

Dummer et al (2018) reported on results of a phase 3 COLUMBUS RCT comparing encorafenib, a *BRAF* inhibitor, alone or in combination with the MEK inhibitor binimetinib, with vemurafenib in patients who had advanced *BRAF* V600−variant unresectable or metastatic melanoma.[25] The COLUMBUS trial was conducted in 162 hospitals in 28 countries between 2013 and 2015; patients were randomized (1:1:1) to oral encorafenib 450 mg once daily plus oral binimetinib 45 mg twice daily (n=192), oral encorafenib 300 mg once daily (n=194), or oral vemurafenib 960 mg twice daily (n=191). The primary outcome was PFS for encorafenib plus binimetinib vs. vemurafenib. Analyses were done on the intention-to-treat population. Median follow-up was 17 months. PFS was significantly increased with encorafenib plus binimetinib compared with vemurafenib (median PFS=14.9 months vs. 7.3 months in the vemurafenib group; HR=0.54; 95% CI, 0.41 to 0.71; p<0.001; see Table 2). The OS was not reported. The most common grade 3 or 4 adverse events were increased γ-glutamyltransferase (9%), increased creatine phosphokinase (7%), and hypertension (6%) in the encorafenib plus binimetinib group; palmoplantar erythrodysesthesia syndrome (14%), myalgia (10%), and arthralgia (9%) in the encorafenib group; and arthralgia (6%) in the vemurafenib group.

Ascierto (2020) et al published long-term outcomes from the COLUMBUS trial (Table 2).[31] The median follow-up for overall survival was 48.8 months. Compared with vemurafenib, the combination of encorafenib plus binimetinib significantly reduced the risk of death by 39% (HR, 0.61; 95% CI, 0.48 to 0.79) and increased the duration of PFS (HR, 0.51; 95% CI, 0.39 to

0.67). The overall survival rates for 3 years were 47%, 41%, and 31% for encorafenib plus binimetinib, encorafenib, and vemurafenib groups, respectively. All subgroup analyses favored combination treatment with encorafenib plus binimetinib versus treatment with vemurafenib alone.

Combination *BRAF*, *MEK*, and Immune Checkpoint Inhibition

Atezolizumab, Vemurafenib, and Cobimetinib

Gutzmer et al (2020) reported primary results from IMspire150, a phase 3, double-blind RCT of atezolizumab, vemurafenib, and cobimetinib (n=256) compared to placebo, vemurafenib, and cobimetinib (n=258) as first-line treatment for unresectable advanced *BRAF* V600-positive melanoma (Table 2).[32] The primary endpoint was investigator-assessed PFS. The median follow-up in the overall study population was 18.9 months. At data cut-off, 327 patients had progressive disease by investigator assessment or had died, including 148 (58%) of patients in the atezolizumab group and 179 (69%) in the control group. The atezolizumab with vemurafenib and cobimetinib group experienced a median PFS per investigator assessment of 15.1 months (95% CI, 0.63 to 0.97) compared to 10.6 months (95% CI, 9.3 to 12.7) in the control group. A 77% concordance rate for progressive disease assessment by study investigators versus independent review committee was reported. The primary reason for discordant results (n=109) was assessment of progressive disease by study investigators but not independent review committee. The prevalence of treatment-related adverse events was comparable between the two groups. PD-L1 expression status was not significantly associated with treatment effect.

Section Summary: Clinical Validity and Clinical Utility

RCTs of *BRAF* and *MEK* inhibitor therapy in patients selected by *BRAF* V600 variant testing have shown improvements in OS and PFS. Single-agent *BRAF* inhibitor treatment with vemurafenib and dabrafenib compared with chemotherapy has shown superior outcomes for response and PFS. Combination *BRAF* and *MEK* inhibitor treatment with vemurafenib plus cobimetinib or dabrafenib plus trametinib have shown superior OS compared with vemurafenib alone or dabrafenib alone. There are no RCTs directly comparing *BRAF* and *MEK* inhibitor therapy with immunotherapy as a first-line treatment for patients with *BRAF* pathogenic variants. Network meta-analyses including indirect comparisons have suggested that *BRAF* and *MEK* combination therapy might prolong PFS but with higher toxicity compared with immunotherapy.

BRAF TESTING IN RESECTED STAGE III MELANOMA

As was stated, clinical validity and clinical utility are evaluated together when treatments are developed for a specific biologic target that characterizes only some patients with a particular disease, and a test is codeveloped to identify diseased patients with that target. Therefore, phase 3 RCTs of targeted treatments are reviewed in this section in which either (1) testing for the *BRAF* variant was required for enrollment into the trial or (2) RCTs in which *both* patients with and without *BRAF* variants were enrolled and treatment effects stratified by variant status are reported.

Clinical Context and Test Purpose

The purpose of testing for *BRAF* pathogenic variants in individuals with resected stage III melanoma is to inform a decision whether to use adjuvant treatment with *BRAF* and/or *MEK* tyrosine kinase inhibitors after surgical resection. Observation, as well as treatment with nivolumab or ipilimumab, are also options for resected, stage III melanoma.

Clinically Valid and Clinically Useful

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Review of Evidence

Two RCTs of *BRAF* and/or *MEK* inhibitors in patients with resected stage III *BRAF* variant melanoma, have been reported. Trial design characteristics are reported in Table 2; results are reported in Table 3. An appraisal of study relevance as well as design and conduct gaps are reported in Tables 4 and 5.

Long et al (2017) reported on results of COMBI-AD, a phase 3 RCT comparing adjuvant combination therapy using dabrafenib plus trametinib with placebo in 870 patients who had stage III melanoma with *BRAF* V600E or V600K variants.[27] In 2013 and 2014 when patients were being enrolled in COMBI-AD, observation was the standard of care after resection of stage III melanoma in most countries. With a median follow-up of 2.8 years, the 3-year rate of relapse-free survival was 58% in the combination group and 39% in the placebo group (HR=0.47; 95% CI, 0.39 to 0.58; p<0.001). The OS rates for 3 years were 86% and 77%, respectively (HR=0.57; 95% CI, 0.42 to 0.79; p<0.001).

Maio et al (2018) reported on results of BRIM8, a phase 3 RCT comparing adjuvant vemurafenib monotherapy with placebo in 498 patients who had stage IIC, IIIA, IIIB, or IIIC *BRAF* V600 variant−positive melanoma.[28] Patients with stage IIC, IIIA, or IIIB disease were enrolled in cohort 1 (n=314), and patients with stage IIIC disease were enrolled in cohort 2 (n=184). As stated previously, during enrollment, observation was standard care for stage III melanoma. A hierarchical testing strategy was prespecified for the primary outcome (disease-free survival) based on the assumption that observing a biologic effect in higher risk disease (i.e., cohort 2) would suggest a treatment effect across the continuum of melanoma given the effect is already established in metastatic melanoma. In the hierarchical strategy, only a p value of 0.05 or less in cohort 2 would allow for results in cohort 1 to be considered significant. The median trial follow-up was 34 months (interquartile range, 26-42 months) in cohort 2 and 31 months (interquartile range, 26-41 months) in cohort 1. In cohort 2, median disease-free survival was 23 months (95% CI, 19 to 27 months) in the vemurafenib group and 15 months (95% CI, 11 to 36 months) in the placebo group (HR=0.80; 95% CI, 0.54 to 1.18; p=0.26). In cohort 1, median disease-free survival was not reached (95% CI, not estimable) in the vemurafenib group and 37 months (95% CI, 21 to not estimable) in the placebo group (HR=0.54; 95% CI, 0.37 to 0.78); however, this result cannot be considered statistically significant because of the prespecified hierarchical testing strategy.

Table 2. Characteristics of RCTs of *BRAF* and/or *MEK* Inhibitors for *BRAF*-Positive Stage III Melanoma

Study/Trial	Countries	Sites	Dates	Participants	Interventions	
					BRAF and/or MEK Inhibitor	Control
Long et al (2017)[27]; COMBI-AD (NCT01682083)	26 countries including US	169	2013-2014	Adults with completely resected stage III melanoma with *BRAF* V600E or V600K variants:	Dabrafenib (150 mg bid) + Trametinib (2 mg qd) for 12 mo (n=438)	Matching placebos (n=432)

				• Stage IIIA: 19% • Stage IIIB: 39% • Stage IIIC: 41% • Stage III unspecified: 1%		

Maio et al (2018)[28]; BRIM8 (NCT01667419)	23 countries including US	124	2012-2015	• Adults with completely resected stage IIC, IIIA, or IIIB (cohort 1) or stage IIIC (cohort 2) melanoma with *BRAF* V600E or V600K variants
				• Cohort 1:
				  ○ Stage IIC: 9%
				  ○ Stage IIIA: 24%
				  ○ Stage IIIB: 68%
				• Cohort 2:
				  ○ Stage IIIC: 100%
					• Cohort 1: n=157
					• Cohort 2: n=93
					• Vemurafenib (960 mg bid) for 12 mo
						• Cohort 1: n=157
						• Cohort 2: n=91
						• Matching placebo

Bid: twice daily; qd: every day; RCT: randomized controlled trial

Table 3. Results of RCTs of *BRAF* and/or *MEK* Inhibitors for *BRAF*-Positive Stage III Melanoma

Study	Median Recurrence-Free Survival, mo	Distant Metastasis	Death	SAEs
	Recurrence or Death	**% Over Study Period**	**% Over Study Period**	
Long et al (2017)[27]				
N	870	870	870	867
Dabrafenib + Trametinib (95% CI)	Not yet reached (44.5 to NE)	25	14	36%
Control (95% CI)	16.6 (12.7 to 22.1)	35	22	10%
TE (95% CI); p	HR=0.47 (0.39 to 0.58); <0.001	HR=0.51 (0.40 to 0.65); <0.001	HR=0.57 (0.42 to 0.79); <0.001	NR
	Recurrence, New Primary Melanoma, or Death	**Median, mo**	**% at 2 Years**	
Maio et al (2018)[28]				
Cohort 1 (stage IIC, IIIA, IIIB)				
N	314	314	314	494[b]
Vemurafenib	Not yet reached (NE)	Not yet reached (NE)	93 (89 to 98)	16%
Control	36.9 (21.4 to NE)	Not yet reached (NE)	87 (81 to 92)	10%
TE (95% CI); p	HR=0.54 (0.37 to 0.78)[a]	HR=0.58 (0.37 to 0.90); 0.01	NR	NR
Cohort 2 (stage IIIC)				
N	184	184	184	See above[b]
Vemurafenib	23.1 (18.6 to 26.5)	37.2 (22.1 to NE)	84 (76 to 92)	
Control	15.4 (11.1 to 35.9)	30.7 (24.5 to NE)	85 (78 to 93)	
TE (95% CI); p	HR=0.80 (0.54 to 1.18); 0.26[a]	HR=0.91 (0.57 to 1.44); 0.68	NR	

CI: confidence interval; HR: hazard ratio; NE: not estimable; NR: not reported; RCT: randomized controlled trial; SAE: serious adverse event; TE: treatment effect.
[a] Hierarchical testing of cohort 2 before cohort 1 was prespecified for this outcome. Because the HR in cohort 2 was not statistically significantly different than 1, the test in cohort 1 cannot be regarded as significant.
[b] Cohorts 1 and 2 combined for safety analyses.

Section Summary: Clinical Valid and Clinically Useful
RCTs of *BRAF* and *MET* inhibitor therapy in stage III melanoma patients selected by *BRAF* V600 variant testing have shown reductions in recurrence risk. One well-conducted RCT of combination *BRAF* and *MEK* inhibitor treatment with dabrafenib plus trametinib has shown superiority for recurrence risk and OS in *BRAF* variant−positive, stage III patients compared with placebo. Single-agent *BRAF* inhibitor treatment using vemurafenib compared with placebo showed numeric benefit for disease-free survival in patients with stage IIC, IIIA, or IIIB *BRAF* V600 variant−positive melanoma but this result must be considered exploratory given the lack of statistically significant benefit in stage IIIC disease and the hierarchical statistical testing strategy. There are no RCTs directly comparing *BRAF* and *MEK* inhibitor therapy with immunotherapy as an adjuvant treatment for stage III patients with *BRAF* pathogenic variants.

Tumor Mutational Burden Testing in Unresectable or Metastatic Melanoma
When treatment is developed for a specific biologic target that characterizes only some patients with a particular disease, and a test is co-developed to identify diseased patients with that target, clinical validity and clinical utility cannot be evaluated separately. Rather, clinical studies of treatment benefits; that use the test to select patients, provide evidence of both clinical validity and clinical utility. We reviewed clinical trials of treatments in which testing for tumor mutational burden (TMB) was required. In the absence of clinical trials in which both patients with and without TMB testing are entered into randomized controlled trials (RCTs) of novel therapies, we cannot be certain that the test has clinical utility because it is unknown whether the treatment would be effective in patients without high TMB. However, phase 3 trials are currently not available.

Review of Evidence

Pembrolizumab
Marabelle et al (2020) reported the association of TMB-high (TMB-H) status to response to pembrolizumab in patients with various previously treated unresectable or metastatic solid tumors enrolled in a prespecified exploratory analysis of the nonrandomized, phase 2 KEYNOTE-158 study (NCT02628067).[33] TMB-H was defined as ≥10 mutations per megabase according to the FoundationOne CDx panel. The proportion of patients with an objective response in the TMB-H group was 29%. At a median follow-up of approximately 3 years, the median duration of response was not reached in the TMB-H group and was 33.1 months in the non-TMB-H group. TMB-H status was associated with improved response irrespective of PD-L1 status. Median PFS and OS did not differ between the high and non-high TMB groups. Objective responses were observed in 24 (35%; 95% CI, 24 to 48) of 68 participants who had both TMB-H status and PD-L1-positive tumors (i.e., PD-L1 combined positive score of ≥1) and in 6 (21%; 8 to 40) of 29 participants who had TMB-H status and PD-L1-negative tumors.

Notably, patients with melanoma or glioma were not included in these analyses. Study eligible cancers were limited to anal, biliary, cervical, endometrial, mesothelioma, neuroendocrine, salivary, small-cell lung, thyroid, and vulvar. The prescribing information for pembrolizumab includes a “Limitation of Use” stating that the safety and effectiveness of pembrolizumab in pediatric patients with TMB-H central nervous system cancers have not been established.

Section Summary: Clinically Valid and Clinically Useful
In a prespecified retrospective subgroup analysis of a nonrandomized trial of pembrolizumab in patients with various solid tumors, 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 PFS survival were not significantly different between TMB groups. These results need to be confirmed in well-designed prospective studies enrolling patients with melanoma and glioma.

NTRK Testing in Melanoma

Clinical Context and Test Purpose

The purpose of testing *NTRK* pathogenic variants in individuals with unresectable or metastatic melanoma is to inform a decision whether to treat *NTRK* inhibitors, alone or in combination with immunotherapy, or with other standard treatments for metastatic melanoma.

Review of Evidence

Lezcano et al (2018), sought to determine the frequency of *NTRK* gene rearrangements in metastasizing melanomas as this could provide an option for targeted therapy if the tumor did not respond to immunotherapy or other available treatments.[34] Seven hundred fifty-one cases were identified, including melanomas of cutaneous (449 total, 395 non-acral, 54 acral), mucosal/paramucosal (113), uveal (70) and primary CNS (2) origin, as well as metastases with unknown primary site (117). Of the 751 lesions, three metastatic melanomas of cutaneous origin and one metastasis from anal primary melanoma were found with *NTRK* fusions.

According to Solomon et al (2019), *NTRK* fusions are characteristic of a few rare types of cancer, such as secretory carcinoma of the breast or salivary gland and infantile fibrosarcoma, but they are also infrequently seen in some common cancers, such as melanoma, glioma and carcinomas of the thyroid, lung and colon.[35] Due to the efficacy of tropomyosin receptor kinase (TRK) inhibitor therapy and the recent Food and Drug Administration approval of larotrectinib, it is now clinically important to accurately and efficiently identify patients with neurotrophic TRK (*NTRK*) fusion-driven cancer. These oncogenic fusions occur when the kinase domain of *NTRK1*, *NTRK2* or *NTRK3* fuse with any of a number of N-terminal partners.

In 2020, Forschner et al. reviewed the available literature for the prevalence of *NTRK* fusion proteins in melanoma cohorts in order to get a percentage that reflects the frequency of *NTRK* fusions in melanoma individuals.[36] The authors found the highest percentage of *NTRK* fusion genes (21% and 28%) in the cohort of spitzoid melanomas. In cutaneous and mucosal melanoma, the prevalence was less than 1%, whereas in acral melanoma NTRK fusion proteins and most common oncogenic drivers such as BRAF, NRAS, HRAS, GNAQ and GNA11 are mutually exclusive, so that *NTRK* fusion proteins might be more common in BRAF or NRAS wild-type melanoma. The authors concluded that *NTRK* inhibitors are a new potential therapeutic option for patients with proven *NTRK* fusion, in particular for patients with a high tumor burden who require rapid tumor regression.

Hong et al (2020), studied the efficacy and long-term safety of Larotrectinib in a larger population of patients with *NTRK* fusion-positive solid tumors.[37] Patients were enrolled and treated in a phase 1 adult, a phase 1/2 pediatric, or a phase 2 adolescent and adult trial. For this pooled analysis, eligible patients were aged 1 month or older, with a locally advanced or metastatic non-CNS primary, TRK fusion-positive solid tumor, who had received standard therapy previously if available. This analysis set includes the 55 patients on which approval of larotrectinib was based. Larotrectinib was administered orally (capsule or liquid formulation), on a continuous 28-day schedule, to adults mostly at a dose of 100 mg twice daily, and to pediatric patients mostly at a dose of 100 mg/m (maximum of 100 mg) twice daily. The primary

endpoint was objective response as assessed by local investigators in an intention-to-treat analysis. One hundred fifty-nine patients with TRK fusion-positive cancer were enrolled and treated with larotrectinib. Ages ranged from less than 1 month to 84 years. The proportion of patients with an objective response according to investigator assessment was 121 (79%,95% CI 72-85) of 153 evaluable patients, with 24 (16%) having complete responses. In a safety population of 260 patients treated regardless of TRK fusion status, the most common grade 3 or 4 larotrectinib-related adverse events were increased alanine aminotransferase (eight [3%] of 260patients), anemia (six, 2%), and decreased neutrophil count (five [2%]). The most common larotrectinib-related serious adverse events were increased alanine aminotransferase (two [<1%] of 260 patients), increased aspartate aminotransferase (two [<1%]), and nausea (two [<1%]). No treatment-related deaths occurred.

Doebele et al (2020), performed an efficacy and safety analysis of patients with metastatic or locally advanced solid tumors harboring oncogenic *NTRK1, NTRK2*, and *NTRK3* gene fusions treated in three ongoing, early-phase trials.[38] The population comprised of 54 adults with advanced or metastatic *NTRK* fusion-positive solid tumors which contained ten different tumor types and 19 different histologies. Median follow-up was 12.9 months (IQR 8・77–18・76). 31 (57%; 95% CI 43・2–70・8). Fifty-four patients had an objective response, of which four (7%) were complete responses and 27 (50%) partial responses. Median duration of response was 10 months (95% CI 7・1 to not estimable). The most common grade 3 or 4 treatment-related adverse events in both safety populations increased weight (seven [10%] of 68 patients in the NTRK fusion-positive safety population and in 18 [5%] of 355 patients in the overall safety-evaluable population) and anemia (8 [12%] and 16 [5%]). The most common serious treatment-related adverse events were nervous system disorders (three [4%] of 68 patients and ten [3%] of 355 patients). No treatment-related deaths occurred.

Section Summary: NTRK Gene Fusions
Two trials have studied the safety and effectiveness of Larotrectinib and Entrectinib in metastatic or locally advanced tumors. Side effects included increased alanine aminotransferase, anemia, and decreased neutrophil count. No treatment-related deaths occurred. Due to the efficacy of tropomyosin receptor kinase (TRK) inhibitor therapy and the recent Food and Drug Administration approval of larotrectinib, it is now clinically important to identify patients accurately and efficiently with neurotrophic TRK (*NTRK*) fusion-driven cancer. Forscher et al (2020) concluded that *NTRK* inhibitors are a new potential therapeutic option for patients with proven *NTRK* fusion, in particular for patients with a high tumor burden who require rapid tumor regression.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network (NCCN)
NCCN guidelines for cutaneous melanoma (v.2.2025) include the following recommendations on somatic genetic testing in cutaneous melanoma.

- 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).
- Repeating 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.
- While the V600E mutation is the most common BRAF mutation, other BRAF mutations exist that may respond equally well to BRAF inhibitors. Some tests have lower sensitivity/specificity or detect only particular mutations. If needed for clinical care, repeat testing using a different methodology may be warranted to detect non-V600E BRAF mutations, or other mutations in different genes. If the initially submitted tissue was of poor quality, a new biopsy may be required before repeat testing is ordered.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
Melanoma			
NCT03155620	NCI-COG pediatric MATCH (molecular analysis for therapy choice) screening protocol	1500	Sep 2027
NCT04722575	NEOadjuvant Plus Adjuvant Therapy with Combination or Sequence of Vemurafenib, cobImetinib, and atezolizuMab in Patients with High-risk, Surgically Resectable BRAF Mutated and Wild-type Melanoma (NEO-TIM)	88	Jun 2027
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, Paediatric 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 Patients 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, Paediatric and Teenage/Young Adult (TYA) Cancers with Actionable Genomic Alterations, Including Common Cancers with Rare Actionable Alterations. Treatment Arm 3:	30	Oct 2029

	Entrectinib in Adult, Teenage/Young Adults and Paediatric Patients with ROS1 Gene Fusion-positive Cancers		
NCT03420508	A Phase 2 Study of the ALK Inhibitor Ensartinib for Patients with Melanomas Harboring ALK Alterations or Aberrant ALK Expression	18	Jan 2026
NCT05767879	Open Label Phase 2 Study Neo-Adjuvant BRAF/MEK Inhibition Followed by Surgery and Adjuvant BRAF/MEK Inhibition in In-transit Melanoma Metastases (NASAM)	28	Jan 2026
Unpublished			
NCT01677741[a]	Phase I/IIa, 2-part, multi-center, single-arm, open-label study to determine the safety, tolerability and pharmacokinetics of oral dabrafenib in children and adolescent subjects with advanced BRAF V600E mutation positive solid tumors	86	May 2020
NCT02034110[a]	A phase II, open-label, study in subjects with BRAF V600E mutated rare cancers with several histologies to investigate the clinical efficacy and safety of the combination therapy of dabrafenib and trametinib	225	Jul 2020

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

Regulatory Status

Table 5 summarizes the targeted treatments approved by the U.S. Food and Drug Administration for patients with melanoma along with the concurrently approved diagnostic tests. The combination agent encorafenib and binimetinib (Array BioPharma) is under review for the treatment of *BRAF* variant advanced, unresectable, or metastatic melanoma with target action date of June 30, 2018. The combination agent of dabrafenib and trametinib (GlaxoSmithKline) was approved in May 2018 for adjuvant treatment of *BRAF* variant, resected, stage III melanoma; the agent had both breakthrough therapy and priority review designations.

Table 5. FDA-Approved Targeted Treatments for Melanoma and Their Approved Companion Diagnostic Tests

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[3]	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.2.2025)[11,]
Atezolizumab and hyaluronidase-tqjs (Tecentriq Hybreza, Genentech)	• 2024: in combination with cobimetinib and vemurafenib for the	No FDA-approved companion diagnostic specific to this formulation is available,	Burotto et al (2023) [15,]	2A or higher/ Cutaneous Melanoma (v.2.2025)[11,]

	treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma as determined by an FDA-approved test	which is intended for subcutaneous injection.	FDA Multi-disciplinary Review and Evaluation (BLA 761347) [16]	
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) • 2024: MI Cancer Seek (Caris Life Sciences)	Dummer et al (2018)[12] Dummer et al (2022)[13]	2A or higher/ Cutaneous Melanoma (v.2.2025)[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) • 2024: MI Cancer Seek (Caris Life Sciences)	Ascierto et al (2016)[14]	2A or higher/ Cutaneous Melanoma (v.2.2025)[11]
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	Melanoma • 2013: THxID™ BRAF kit (bioMérieux) • 2017: FoundationOne CDx™ (Foundation Medicine) • 2024: MI Cancer Seek (Caris Life Sciences)	Hauschild et al (2012)[15] Long et al (2015)[16] Long et al (2014)[17] Robert et al (2015)[18] Long et al (2017)[19]	2A or higher/ Cutaneous Melanoma (v.2.2025)[11]

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) • 2021: FoundationOne CDx	Ascierto et al (2020)[22,]	2A or higher/ Cutaneous Melanoma (v.2.2025)[11,]
Entrectinib (Rozyltrek®; Genentech)[1,4]	• 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		2A or higher/ Cutaneous Melanoma (v.2.2025)[11,]
Larotrectinib (Vitrakvi®; Loxo Oncology/Bayer)[1,4]	• 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.2.2025)[11,]
Pembrolizumab (Keytruda®; Merck)[1,2]	• 2020: treatment of adult and pediatric patients with unresectable or metastatic tumor mutation burden-high (TMB-H) [≥10 mutations/megabase] solid tumors, which have progressed following prior treatment and	• 2020: FoundationOne CDx™ (Foundation Medicine)		2A or higher/ Cutaneous Melanoma (v.2.2025)[11,]

	who have no satisfactory treatment options			
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.2.2024)[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	• 2013: THxID™ BRAF kit (bioMérieux) • 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,]	2A or higher/ Cutaneous Melanoma (v.2.2024)[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) • 2024: MI Cancer Seek (Caris Life Sciences)	Chapman et al (2017)[40]	2A or higher/ Cutaneous Melanoma (v.2.2025)

BRAF: b-raf proto-oncogene, serine/threonine kinase; FDA: Food and Drug Administration; NCCN: National Comprehensive Cancer Network; NTRK: Neurotrophic tyrosine receptor kinase; PD-L1: programmed death-ligand 1; TMB: tumor mutational burden; 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] Use of TRK inhibitors in NTRK gene fusion-positive solid tumors is addressed separately in evidence review 5.01.31.

[51] Please consult the FDA list of 'Cleared or Approved Companion Diagnostic Devices' for most current information.[9,]

FDA product code: OWD.

Government Regulations
National:

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:[57]

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 (e.g., 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.

Local:

LCD A55161, MolDX: FDA-Approved *BRAF* Tests. Effective on or after 07/27/2023.
Two tests have met the FDA criteria for *BRAF* genetic testing:

1. Effective 09/07/2012.
   cobas® 4800 *BRAF V600* to detect the presence of a mutation in the *BRAF* gene in melanoma cells and determine if a patient is eligible for Zelboraf ™(vemurafenib), a treatment indicated for a melanoma that cannot be surgically excised or has spread in the body.
2. Effective 5/29/13.
   ThxID™ *BRAF* V600/K to detect the *BRAF V600E* and *V600K* mutations in selecting melanoma patients whose tumors carry the *BRAF V600E* mutation for treatment with dabrafenib [Tafinlar®] and as an aid in selecting melanoma patients whose tumors carry the *BRAF V600E* or *V600K* mutation for treatment with trametinib [Mekinist™].

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Somatic biomarkers (including liquid biopsy) for targeted treatment and immunotherapy in metastatic colorectal cancer (KRAS, NRAS, BRAF, NTRK, and TMB)
- Bone Marrow Transplantation for Malignant Astrocytomas and Gliomas, Autologous
- GT-Analysis of MGMT Promoter Methylation in Malignant Gliomas

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through September 2025, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/18	8/21/18	8/21/18	Joint policy established
11/1/19	8/20/19		Routine policy maintenance. No change in policy status. Added code 81445 as payable.
1/1/21	12/11/20		Rationale reorganized, some references removed and new references #60 and 61 added. Additions to MPS: Genetic testing using a panel (5 to 50 genes) may be considered appropriate when the type of glioma is uncertain to select appropriate therapy. Testing for genetic mutations using a panel with 5-50 genes may also be considered appropriate for cutaneous melanoma (stage 3 and stage 4) Testing for BRAF V600 or the above panel with 5-50 genes for all other reasons is experimental/investigational. Removed all references to glioma.
1/1/22	10/19/21		Language on TMB not added at this time, pending meeting with Dr. Brown. No changes to policy status.
1/1/23	10/18/22		Routine policy maintenance, no change in status.
1/1/24	10/26/23		Added “including liquid biopsy” to title. Added codes 81455, 81456, 0037U, 0242U, 0239U and 0326U as established. Added language to MPS regarding liquid biopsy approval. Also added statement to MPS of approval of panel testing for more than 51 genes. Vendor managed: N/A (ds)
1/1/25	10/17/24		Added NTRK fusion to title, MPS and rationale section, removed bullets from MPS, added to exclusions, added references 34-39. Codes

			81191-81194 added as established. Vendor managed: N/A (ds)
1/1/26	10/21/25		Routine policy maintenance, added reference #40. Added code 0211U as established. Vendor managed: N/A (ds)

Next Review Date: 4th Qtr. 2026

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING—BRAF/NTRK MUTATION IN SELECTING MELANOMA PATIENTS FOR TARGETED THERAPY INCLUDING LIQUID BIOPSY

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered per policy guidelines
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.