Genetic Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320
Original Effective Date: 11/16/2011
Current Effective Date: 10/11/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

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

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

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider testing for BRAF V600 variants in tumor tissue of patients with unresectable or metastatic melanoma to select patients for treatment with Food and Drug Administration (FDA) approved BRAF inhibitors, MEK inhibitors, or immunotherapy to be **eligible for coverage.****

Based on review of available data, the Company may consider testing for BRAF V600 variants in tumor tissue of patients with resected stage III melanoma to select patients for treatment with Food and Drug Administration (FDA) approved BRAF or MEK inhibitors to be **eligible for coverage.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

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Based on review of available data, the Company considers testing for BRAF V600 variants for all other patients with melanoma to be **investigational.***

Based on review of available data, the Company considers testing for BRAF V600 variants in patients with glioma to select patients for targeted treatment to be **investigational.***

Based on review of available data, the Company considers testing for tumor mutational burden (TMB) in patients with unresectable or metastatic melanoma or glioma to select patients for treatment with Food and Drug Administration-approved immunotherapy to be **investigational.***

Background/Overview

Melanoma

Overall incidence rates for melanoma have been increasing for at least 30 years. In advanced (stage IV) melanoma, the disease has spread beyond the original area of skin and nearby lymph nodes. Although only a small proportion of cases are stage IV at diagnosis, the prognosis is extremely poor; 5-year survival is 15% to 20%.

Variants in the *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. 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 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.

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 are kinase inhibitors of TRK A, B, and C protein. However, entrectinib additionally inhibits 2 other kinases: anaplastic lymphoma kinase and proto-oncogene tyrosine-protein kinase.

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

Glioma

Gliomas encompass a heterogeneous group of tumors and the classification of gliomas has changed over time. In 2016, the World Health Organization (WHO) updated its classification of gliomas based on both histopathologic appearance and molecular parameters. The classification ranges from grade I to IV, corresponding to the degree of malignancy (aggressiveness), with WHO grade I being least aggressive and grade IV being most aggressive.

There is considerable interest in targeted therapies that inhibit the RAF-MEK-ERK pathway, particularly in patients with high-grade and low-grade gliomas whose tumors are in locations that prevent full resection. Evidence from early-phase trials in patients with *BRAF* variant-positive melanoma with brain metastases have suggested some efficacy for brain tumor response with vemurafenib and dabrafenib. indicating that these agents might be potential therapies for primary brain tumors.

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

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

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Table 1 summarizes the targeted treatments approved by the U.S. FDA for patients with melanoma along with the concurrently approved diagnostic tests.

The FDA maintains a list of 'Cleared or Approved Companion Diagnostic Devices'.

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

Treatment	Indication	FDA Approval of Companion Diagnostic Test
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, that have progressed following prior treatment and who have no satisfactory treatment options	• 2020: FoundationOne CDx™‡ (Foundation Medicine)

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)
Entrectinib (Rozyltrek®‡; Genentech)[1]	• 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
Larotrectinib (Vitrakvi®‡; Loxo Oncology/Bayer)[1]	• 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	• 2020: FoundationOne CDx™‡ (Foundation Medicine)

	treatments or whose cancer has progressed following treatment	
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)
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	• 2013: THxID™ ‡BRAF kit (bioMérieux) • 2017: FoundationOne CDx™‡ (Foundation Medicine)
Trametinib (Mekinist™‡; GlaxoSmithKline)	• 2013: treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K variants • 2014: Used in combination with dabrafenib to treat patients with	• 2013: THxID™‡ BRAF kit (bioMérieux) • 2017: FoundationOne CDx™‡

	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	(Foundation Medicine)
Cobimetinib (Cotellic®‡; Genentech)	• 2015: Used in combination with vemurafenib to treat patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K variants	• 2017: FoundationOne CDx™‡ (Foundation Medicine)
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)
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)

FDA: Food and Drug Administration.
[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.
FDA product code: OWD.

Rationale/Source

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. BRAF and MEK inhibitors, alone or in combination with checkpoint inhibitors, are drugs designed to target a somatic variant in the *BRAF* gene. BRAF and MEK inhibitors were originally developed for patients with advanced melanoma. *BRAF* encodes a kinase component in the RAF-MEK-ERK signal transduction phosphorylation cascade. Variants in *BRAF* cause constitutive kinase activity, which is believed to promote oncogenic proliferation. Direct and specific inhibition of the mutated kinase has been shown to retard tumor growth significantly and may improve patient survival. Checkpoint inhibitors are monoclonal antibodies that were initially developed to target tumors expressing high levels of PD-L1. Tumors with a high TMB may also predict benefit from checkpoint inhibitor immunotherapy.

Summary of Evidence

For individuals who have unresectable or metastatic melanoma who receive *BRAF* gene variant testing to select a treatment with BRAF inhibitors, MEK inhibitors, or immunotherapy , the evidence includes randomized trials. Relevant outcomes are overall survival (OS), disease-specific survival, and test accuracy. Randomized phase 3 trials of BRAF inhibitor therapy in patients selected on the basis of *BRAF* variant testing have shown improvements in OS and progression-free survival. Single-agent BRAF inhibitor treatment compared with nontargeted treatments has shown superior outcomes for most endpoints. Combination BRAF and MEK inhibitor treatment with vemurafenib plus cobimetinib or dabrafenib plus trametinib have shown superior OS compared with vemurafenib or dabrafenib alone. Data showing treatment effects in patients without *BRAF* variants do not exist; therefore, *BRAF* variant testing is required to identify patients to whom these trial results apply. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have resected stage III melanoma who receive *BRAF* gene variant testing to select a treatment with BRAF or MEK inhibitors, the evidence includes randomized trials. Relevant outcomes are OS, disease-specific survival, and test accuracy. One randomized phase 3 trial of

BRAF and MEK combination therapy with dabrafenib plus trametinib in patients selected by *BRAF* variant testing has shown improvements in recurrence-free survival and OS compared with placebo. One randomized phase 3 trial of vemurafenib monotherapy did not find statistically significant differences in disease-free survival in patients with stage IIIC disease. In patients with stage IIC, IIIA, or IIIB disease, median disease-free survival was prolonged with vemurafenib, but this result was considered exploratory. Data showing treatment effects in patients without *BRAF* variants do not exist; therefore, *BRAF* variant testing is required to identify patients to whom these trial results apply. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have glioma who receive *BRAF* gene variant testing to select a treatment with BRAF or MEK inhibitors, the evidence includes small, prospective, uncontrolled studies and case reports. Relevant outcomes are OS, disease-specific survival, and test accuracy. Studies assessing the use of sorafenib in patients with newly diagnosed and recurrent gliomas combined with various other treatments have not shown benefit, although most did not report *BRAF* V600 variant status. Evaluation of the BRAF and MEK inhibitors vemurafenib, dabrafenib, and trametinib in patients with gliomas has been limited "basket" studies. Selumetinib is being investigated in pediatric, low-grade glioma. Confirmatory randomized controlled trials are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have unresectable or metastatic melanoma or glioma who receive TMB testing to select treatment with immunotherapy, the evidence includes a prespecified retrospective subgroup analysis of a nonrandomized phase 2 trial. Relevant outcomes are OS, disease-specific survival, and test accuracy. Objective responses were observed in 35% of participants who had both TMB-high status and PD-L1-positive tumors and in 21% of participants who had TMB-high status and PD-L1-negative tumors. TMB-high status was associated with improved response irrespective of PD-L1 status. Median OS and PFS survival were not significantly different between TMB groups. Patients with melanoma and glioma were not enrolled in the study. Well-designed prospective studies enrolling patients in the population of interest are required. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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
The National Comprehensive Cancer Network guidelines for cutaneous melanoma (v.2.2021) recommends *BRAF* mutation testing for patients with stage IIIB microscopic satellite disease if adjuvant therapy or clinical trial enrollment is being considered. *BRAF* mutation testing is also recommended for patients who are sentinel node-positive and stage IIIB/C/D and the consideration of *BRAF* mutation testing for sentinel node-positive stage IIIA. The guidelines recommend *BRAF* mutation testing for clinically node-positive or clinical satellite/in-transit stage III. For stage IV patients, the guidelines recommend *BRAF* mutation testing if not previously performed. The guidelines state the use of mutation burden to guide treatment decisions remains investigational at this time.

Network guidelines for central nervous system cancers (v.5.2020) indicate the following on the use of *BRAF* molecular markers to guide treatment decisions for primary brain cancers: "*BRAF* V600E tumors may respond to BRAF inhibitors such as vemurafenib, but comprehensive clinical trials are still ongoing." The guidelines state that BRAF and MEK inhibitors can be considered for pilocytic astrocytoma, pleomorphic xanthoastrocytoma, or ganglioglioma with a *BRAF* V600E activating mutation. The guidelines do not discuss tumor mutation burden testing.

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

Medicare National Coverage
In January 2020, the Centers for Medicare and Medicaid Services (CMS) determined that next generation sequencing (NGS) is covered for patients with somatic (acquired) cancer when the diagnostic test is performed in a CLIA-(Clinical Laboratory Improvement Amendments) certified

laboratory, when ordered by a treating physician, and when all of the following requirements are met:

a. Patient has:
    i. either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and
    ii. not been previously tested with the same test using NGS for the same cancer genetic content, and
    iii. decided to seek further cancer treatment (eg, therapeutic chemotherapy).
b. The diagnostic laboratory test using NGS must have:
    i. FDA approval or clearance as a companion in vitro diagnostic; and,
    ii. an FDA-approved or -cleared indication for use in that patient's cancer; and,
    iii. results provided to the treating physician for management of the patient using a report template to specify treatment options.

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

Ongoing and Unpublished Clinical Trials
Some currently ongoing or unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
Melanoma			
NCT02553642[a]	A Prospectively Designed Study to Assess the Relationship Between Tumor Mutation Burden and Predicted Neo-antigen Burden in Patients With Advanced Melanoma or Bladder Cancer Treated	81	Sep 2021

	With Nivolumab or Nivolumab Plus Ipilimumab (CA209-260)		
NCT02967692[a]	A Randomized, Double-blind, Placebo-controlled, Phase III Study Comparing the Combination of PDR001, Dabrafenib and Trametinib Versus Placebo, Dabrafenib and Trametinib in Previously Untreated Patients With Unresectable or Metastatic BRAF V600 Mutant Melanoma	569	Jul 2023
NCT04309409	Adjuvant Nivolumab Treatment in Stage II High-risk Melanoma - A Randomized, Controlled, Phase III Trial With Biomarker-based Risk Stratification	374	Jun 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
Glioma			
NCT02617589[a]	A Randomized Phase 3 Open Label Study of Nivolumab vs Temozolomide Each in Combination With Radiation Therapy in Newly Diagnosed Adult Subjects With Unmethylated MGMT (Tumor O-6-methylguanine DNA Methyltransferase) Glioblastoma (CheckMate 498: CHECKpoint Pathway and Nivolumab Clinical Trial Evaluation 498)	560	Aug 2021
NCT01089101	A Phase 1 and Phase II and Re-Treatment Study of AZD6244 for Recurrent or Refractory Pediatric Low Grade Glioma	220	Dec 2025
NCT01748149[a]	PNOC-002: Safety, Phase 0, and Pilot Efficacy Study of Vemurafenib, an Oral Inhibitor	40	Jan 2022

	of *BRAF* V600E, in Children and Young Adults With Recurrent/Refractory *BRAF*V600E- or *BRAF* Ins T Mutant Brain Tumors		
NCT02285439	Phase I Study of MEK162 for Children With Progressive or Recurrent Cancer and a Phase II Study for Children With Low-Grade Gliomas and Other Ras/Raf/MAP Pathway Activated Tumors	105	Feb 2023
NCT03973918[a]	A Phase II Study of Binimetinib in Combination With Encorafenib in Adults With Recurrent BRAF V600-Mutated High-Grade Astrocytoma or Other Primary Brain Tumor	62	Jul 2023
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	206	Aug 2021
NCT02465060	Molecular Analysis for Therapy Choice (MATCH)	6452	Jun 2022
NCT03220035	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice)- Phase 2 Subprotocol of Vemurafenib in Patients With Tumors Harboring *Braf* V600 Mutations	49	Dec 2023
NCT02684058[a]	Phase II Open-label Global Study to Evaluate the Effect of Dabrafenib in Combination With Trametinib in Children and Adolescent Patients With *BRAF* V600 Mutation Positive Low Grade Glioma (LGG) or Relapsed or Refractory High Grade Glioma (HGG)	150	Oct 2025
NCT04166409	A Phase 3 Randomized Non-Inferiority Study of Carboplatin and Vincristine Versus Selumetinib (NSC# 748727) in Newly Diagnosed or Previously	220	Dec 2026

	Untreated Low-Grade Glioma (LGG) Not Associated With *BRAF* V600E Mutations or Systemic Neurofibromatosis Type 1 (NF1)		
NCT03155620	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol	1500	Sep 2027

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

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Policy History

Original Effective Date: 11/16/2011
Current Effective Date: 10/11/2021

11/03/2011	Medical Policy Committee review
11/16/2011	Medical Policy Implementation Committee approval. New policy.
11/01/2012	Medical Policy Committee review
11/28/2012	Medical Policy Implementation Committee approval. "Targeted" added to the title. Eligible for coverage statement modified to read "FDA-approved BRAF inhibitors" in place of "vemurafenib" .
12/12/2013	Medical Policy Committee review
12/18/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2015	Coding Update
01/08/2015	Medical Policy Committee review
01/21/2015	Medical Policy Implementation Committee approval. New policy.
01/07/2016	Medical Policy Committee review
01/22/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
01/05/2017	Medical Policy Committee review
01/18/2017	Medical Policy Implementation Committee approval. No change to coverage.
10/05/2017	Medical Policy Committee review
10/18/2017	Medical Policy Implementation Committee approval. Policy revised with updated genetics nomenclature. Policy statements regarding BRAF testing in melanoma unchanged. Information about FDA-approved MEK inhibitor (cobimetinib) added. New policy statement stating BRAF testing in glioma is investigational was added. Policy title changed to "BRAF Gene Mutation Testing to Select Melanoma or Glioma Patients for Targeted Therapy".
08/09/2018	Medical Policy Committee review

Genetic Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320
Original Effective Date: 11/16/2011
Current Effective Date: 10/11/2021

08/15/2018	Medical Policy Implementation Committee approval. New policy statement added stating BRAF testing in resected, stage III melanoma is eligible for coverage. "Mutation" changed to "variant" in policy title.
08/01/2019	Medical Policy Committee review
08/14/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/06/2020	Medical Policy Committee review
08/12/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/02/2021	Medical Policy Committee review
09/08/2021	Medical Policy Implementation Committee approval. New policy statement stating TMB testing in melanoma and glioma is investigational was added. Policy title changed to "Genetic Testing to Select Melanoma or Glioma Patients for Targeted Therapy."

Next Scheduled Review Date: 09/2022

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2020 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Genetic Testing to Select Melanoma or Glioma Patients for Targeted Therapy

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contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

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

Code Type	Code
CPT	81210
HCPCS	No codes
ICD-10 Diagnosis	C43.0-C43.9, D03.0-D03.9

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment,

would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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

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

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.