

BRAF Mutation Analysis

Last Review Date: December 10, 2021

Number: MG.MM.LA.38d

Medical Guideline Disclaimer

Property of EmblemHealth. All rights reserved. The treating physician or primary care provider must submit to EmblemHealth the clinical evidence that the patient meets the criteria for the treatment or surgical procedure. Without this documentation and information, EmblemHealth will not be able to properly review the request for prior authorization. The clinical review criteria expressed below reflects how EmblemHealth determines whether certain services or supplies are medically necessary. EmblemHealth established the clinical review criteria based upon a review of currently available clinical information (including clinical outcome studies in the peer reviewed published medical literature, regulatory status of the technology, evidence-based guidelines of public health and health research agencies, evidence-based guidelines and positions of leading national health professional organizations, views of physicians practicing in relevant clinical areas, and other relevant factors). EmblemHealth expressly reserves the right to revise these conclusions as clinical information changes and welcomes further relevant information. Each benefit program defines which services are covered. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered and/or paid for by EmblemHealth, as some programs exclude coverage for services or supplies that EmblemHealth considers medically necessary. If there is a discrepancy between this guideline and a member's benefits program, the benefits program will govern. In addition, coverage may be mandated by applicable legal requirements of a state, the Federal Government or the Centers for Medicare & Medicaid Services (CMS) for Medicare and Medicaid members. All coding and web site links are accurate at time of publication. EmblemHealth Services Company LLC, ("EmblemHealth") has adopted the herein policy in providing management, administrative and other services to EmblemHealth Plan, Inc., EmblemHealth Insurance Company, EmblemHealth Services Company, LLC and Health Insurance Plan of Greater New York (HIP) related to health benefit plans offered by these entities. All of the aforementioned entities are affiliated companies under common control of EmblemHealth Inc.

Definition

BRAF gene (serine/threonine-protein kinase B-Raf, v-raf murine sarcoma viral oncogene homolog B1), is an oncogene that encodes a protein kinase, which is part of the RAS/MAPK signaling pathway that regulates intracellular signaling and mediates cell growth, division, differentiation, cell movement and self-destruction. It is a principle downstream effector of NRAS and KRAS.

BRAF gene mutations are seen most commonly in melanoma, but have also been found in acute leukemias, lymphoma, colon, lung and thyroid cancer. BRAF gene mutations occur in less than 15% of colorectal cancers and approximately 50% of cutaneous melanomas.

Related Medical Guidelines

[Analysis of KRAS Status](#)

[Genetic Testing for Colorectal Cancer](#)

Guideline

BRAF mutation analysis in tumor tissue of members with Langerhans Cell Histiocytosis, Erdheim Chester Disease (ECD), unresectable or metastatic melanoma, metastatic colorectal cancer, non-small cell lung cancer, thyroid cancer or hairy cell leukemia is considered medically necessary to select those who would benefit from treatment with an FDA-approved BRAF inhibitor.

Limitations/Exclusions

BRAF mutation analysis is considered investigational and not medically necessary for all other indications that do not meet the criteria above.

Results will help select or maintain therapy.

Revision History

Dec. 12, 2021	Added note communicating that results must impact therapeutic decision-making
Dec. 11, 2020	Added thyroid cancer as covered indication

Oct. 11, 2019	Added Langerhans Cell Histiocytosis, Erdheim Chester Disease (ECD) as covered indications (eff. Jan. 11, 2020)
Oct. 14, 2016	Added non-small cell lung cancer and hairy cell leukemia as covered indications.

Applicable Procedure Codes

81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
88363	Examination and selection of retrieved archival (ie, previously diagnosed) tissue(s) for molecular analysis (e.g., KRAS mutational analysis) [when specified in relation to BRAF testing]

Applicable ICD-10 Diagnosis Codes

C17.0	Malignant neoplasm of duodenum
C17.1	Malignant neoplasm of jejunum
C17.2	Malignant neoplasm of ileum
C17.3	Meckel's diverticulum, malignant
C17.8	Malignant neoplasm of overlapping sites of small intestine
C17.9	Malignant neoplasm of small intestine, unspecified
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.1	Malignant neoplasm of anal canal
C21.2	Malignant neoplasm of cloacogenic zone
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C33	Malignant neoplasm of trachea
C34.00	Malignant neoplasm of unspecified main bronchus
C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus
C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung

C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung
C43.0	Malignant melanoma of lip
C43.10	Malignant melanoma of unspecified eyelid, including canthus
C43.111	Malignant melanoma of right upper eyelid, including canthus
C43.112	Malignant melanoma of right lower eyelid, including canthus
C43.121	Malignant melanoma of left upper eyelid, including canthus
C43.122	Malignant melanoma of left lower eyelid, including canthus
C43.20	Malignant melanoma of unspecified ear and external auricular canal
C43.21	Malignant melanoma of right ear and external auricular canal
C43.22	Malignant melanoma of left ear and external auricular canal
C43.30	Malignant melanoma of unspecified part of face
C43.31	Malignant melanoma of nose
C43.39	Malignant melanoma of other parts of face
C43.4	Malignant melanoma of scalp and neck
C43.51	Malignant melanoma of anal skin
C43.52	Malignant melanoma of skin of breast
C43.59	Malignant melanoma of other part of trunk
C43.60	Malignant melanoma of unspecified upper limb, including shoulder
C43.61	Malignant melanoma of right upper limb, including shoulder
C43.62	Malignant melanoma of left upper limb, including shoulder
C43.70	Malignant melanoma of unspecified lower limb, including hip
C43.71	Malignant melanoma of right lower limb, including hip
C43.72	Malignant melanoma of left lower limb, including hip
C43.8	Malignant melanoma of overlapping sites of skin
C43.9	Malignant melanoma of skin, unspecified
C44.1021	Unspecified malignant neoplasm of skin of right upper eyelid, including canthus
C44.1022	Unspecified malignant neoplasm of skin of right lower eyelid, including canthus
C44.1091	Unspecified malignant neoplasm of skin of left upper eyelid, including canthus
C44.1092	Unspecified malignant neoplasm of skin of left lower eyelid, including canthus
C44.1921	Other specified malignant neoplasm of skin of right upper eyelid, including canthus
C44.1922	Other specified malignant neoplasm of skin of right lower eyelid, including canthus
C44.1991	Other specified malignant neoplasm of skin of left upper eyelid, including canthus
C44.1992	Other specified malignant neoplasm of skin of left lower eyelid, including canthus
C73	Malignant neoplasm of thyroid gland
C77.0	Secondary and unspecified malignant neoplasm of lymph nodes of head, face and neck
C77.1	Secondary and unspecified malignant neoplasm of intrathoracic lymph nodes

C77.2	Secondary and unspecified malignant neoplasm of intra-abdominal lymph nodes
C77.3	Secondary and unspecified malignant neoplasm of axilla and upper limb lymph nodes
C77.4	Secondary and unspecified malignant neoplasm of inguinal and lower limb lymph nodes
C77.5	Secondary and unspecified malignant neoplasm of intrapelvic lymph nodes
C77.8	Secondary and unspecified malignant neoplasm of lymph nodes of multiple regions
C77.9	Secondary and unspecified malignant neoplasm of lymph node, unspecified
C78.00	Secondary malignant neoplasm of unspecified lung
C78.01	Secondary malignant neoplasm of right lung
C78.02	Secondary malignant neoplasm of left lung
C78.1	Secondary malignant neoplasm of mediastinum
C78.2	Secondary malignant neoplasm of pleura
C78.30	Secondary malignant neoplasm of unspecified respiratory organ
C78.39	Secondary malignant neoplasm of other respiratory organs
C78.4	Secondary malignant neoplasm of small intestine
C78.5	Secondary malignant neoplasm of large intestine and rectum
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C78.80	Secondary malignant neoplasm of unspecified digestive organ
C78.89	Secondary malignant neoplasm of other digestive organs
C79.00	Secondary malignant neoplasm of unspecified kidney and renal pelvis
C79.01	Secondary malignant neoplasm of right kidney and renal pelvis
C79.02	Secondary malignant neoplasm of left kidney and renal pelvis
C79.10	Secondary malignant neoplasm of unspecified urinary organs
C79.11	Secondary malignant neoplasm of bladder
C79.19	Secondary malignant neoplasm of other urinary organs
C79.2	Secondary malignant neoplasm of skin
C79.31	Secondary malignant neoplasm of brain
C79.32	Secondary malignant neoplasm of cerebral meninges
C79.40	Secondary malignant neoplasm of unspecified part of nervous system
C79.49	Secondary malignant neoplasm of other parts of nervous system
C79.51	Secondary malignant neoplasm of bone
C79.52	Secondary malignant neoplasm of bone marrow
C79.60	Secondary malignant neoplasm of unspecified ovary
C79.61	Secondary malignant neoplasm of right ovary
C79.62	Secondary malignant neoplasm of left ovary
C79.70	Secondary malignant neoplasm of unspecified adrenal gland
C79.71	Secondary malignant neoplasm of right adrenal gland
C79.72	Secondary malignant neoplasm of left adrenal gland
C79.81	Secondary malignant neoplasm of breast
C79.82	Secondary malignant neoplasm of genital organs
C79.89	Secondary malignant neoplasm of other specified sites
C79.9	Secondary malignant neoplasm of unspecified site
C91.40	Hairy cell leukemia not having achieved remission

C91.41	Hairy cell leukemia, in remission
C91.42	Hairy cell leukemia, in relapse
C96.6	Unifocal Langerhans-cell histiocytosis (coverage eff. 01/11/2020)
D03.0	Melanoma in situ of lip
D03.10	Melanoma in situ of unspecified eyelid, including canthus
D03.111	Melanoma in situ of right upper eyelid, including canthus
D03.112	Melanoma in situ of right lower eyelid, including canthus
D03.121	Melanoma in situ of left upper eyelid, including canthus
D03.122	Melanoma in situ of left lower eyelid, including canthus
D03.20	Melanoma in situ of unspecified ear and external auricular canal
D03.21	Melanoma in situ of right ear and external auricular canal
D03.22	Melanoma in situ of left ear and external auricular canal
D03.30	Melanoma in situ of unspecified part of face
D03.39	Melanoma in situ of other parts of face
D03.4	Melanoma in situ of scalp and neck
D03.51	Melanoma in situ of anal skin
D03.52	Melanoma in situ of breast (skin) (soft tissue)
D03.59	Melanoma in situ of other part of trunk
D03.60	Melanoma in situ of unspecified upper limb, including shoulder
D03.61	Melanoma in situ of right upper limb, including shoulder
D03.62	Melanoma in situ of left upper limb, including shoulder
D03.70	Melanoma in situ of unspecified lower limb, including hip
D03.71	Melanoma in situ of right lower limb, including hip
D03.72	Melanoma in situ of left lower limb, including hip
D03.8	Melanoma in situ of other sites
D03.9	Melanoma in situ, unspecified
E88.2	Lipomatosis, not elsewhere classified (coverage eff. 01/11/2020)
E88.81	Metabolic syndrome (coverage eff. 01/11/2020)
E88.89	Other specified metabolic disorders (coverage eff. 01/11/2020)
E88.9	Metabolic disorder, unspecified (coverage eff. 01/11/2020)
Z85.038	Personal history of other malignant neoplasm of large intestine
Z85.048	Personal history of other malignant neoplasm of rectum, rectosigmoid junction, and anus
Z85.820	Personal history of malignant melanoma of skin

References

1. Arkenau HT, Kefford R, Long GV. Targeting BRAF for patients with melanoma. *Br J Cancer*. 2011; 104(3):392-398.
2. Bokemeyer C, Kohne C, Rougier P, et al. Cetuximab with chemotherapy (CT) as first-line treatment for metastatic colorectal cancer (mCRC): analysis of the CRYSTAL and OPUS studies according to KRAS and BRAF mutation status. *J Clin Oncol* 2010; 28:15s. (Abstr 3506).
3. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011; 364(26):2507-2516
4. Davies H, Bignell GR, Cox C, Stephens P, et al. Mutations of the BRAF gene in human cancer. *Nature*. 2002; 417(6892):949-954.

5. De Roock W, Claes B, Bernasconi D, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. *Lancet Oncol* 2010; 11: 753–762.
6. Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. *J Clin Oncol*. 2008; 26(35):5705-5712.
7. Flaherty KT, Puzanov I, Kim KB et al. Inhibition of mutated, activated BRAF in metastatic melanoma. *N Engl J Med* 2010; 363(9):809-19.
8. King AJ, Patrick DR, Batorsky RS et al. Demonstration of a genetic therapeutic index for tumors expressing oncogenic BRAF by the kinase inhibitor SB-590885. *Cancer Res* 2006; 66(23):11100-5.
9. Laurent-Puig P, Cayre A, Manceau G, et al. Analysis of PTEN, BRAF, and EGFR status in determining benefit from cetuximab therapy in wild-type KRAS metastatic colon cancer. *J Clin Oncol*. 2009; 27(35):5924–5930
10. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Melanoma: Cutaneous. V2.2021. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma_blocks.pdf. Accessed December 15, 2021.
11. National Government Services. Local Coverage Article. Billing and Coding: Molecular Pathology Procedures. July 2020. <https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35000&ver=119&Date=&DocID=L35000&bc=iAAAABABAAAA&>. Accessed December 15, 2021.
12. Shahabi V, Whitney G, Hamid O, et al. Assessment of association between BRAF-V600E mutation status in melanomas and clinical response to ipilimumab. *Cancer Immunol Immunother*. 2012; 61(5):733-737.
13. Sharma SG, Gulley ML. BRAF mutation testing in colorectal cancer. *Arch Pathol Lab Med*. 2010; 134(8):1225-1228.
14. Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N Engl J Med*. 2012; 366(8):707-714.
15. Van Cutsem E, Kohne CH, Lang I, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol*. 2011; 29(15):2011-2019