HIGHMARK Delaware HEALTH OPTIONS

CLINICAL MEDICAL POLICY	
Policy Name:	BRAF Mutation Analysis
Policy Number:	MP-062-MD-DE
Approved By:	Medical Management
Provider Notice Date:	10/02/2019; 09/01/2018; 11/01/2017
Original Effective Date:	11/04/2019; 10/01/2018; 12/01/2017
Annual Approval Date:	09/10/2020
Revision Date:	09/10/2019; 08/15/2018
Products:	Delaware Medicaid
Application:	All participating hospitals and providers
Page Number(s):	1 of 8

DISCLAIMER

Delaware Highmark Health Options medical policy is intended to serve only as a general reference resource regarding coverage for the services described. This policy does not constitute medical advice and is not intended to govern or otherwise influence medical decisions.

POLICY STATEMENT

Highmark Health Options may provide coverage under the medical-surgical benefits of the Company's Medicaid products for medically necessary BRAF testing for melanoma and colorectal cancer.

This policy is designed to address medical necessity guidelines that are appropriate for the majority of individuals with a particular disease, illness or condition. Each person's unique clinical circumstances warrant individual consideration, based upon review of applicable medical records.

The qualifications of the policy will meet the standards of the National Committee for Quality Assurance (NCQA) and the Delaware Department of Health and Social Services (DHSS) and all applicable state and federal regulations.

DEFINITIONS

BRAF (serine/threonine-protein kinase B-Raf, v-Raf murine sarcoma viral oncogene homolog B1) –
The BRAF gene is located on chromosome arm 7q34. It encodes B-Raf, a serine/threonine kinase that is part of the Ras-Raf-Mek-Erk-MAPK signaling cascade. Changes or mutations to the BRAF gene can cause uncontrolled cell growth, which may lead cancer.

BRAF V600E Mutation – The most common BRAF mutation which accounts for 70% to 90% of mutations.

BRAF V600K Mutation – The second most common BRAF mutation (16%) that passes along the cell growth signal.

Pharmacogenomics – The science concerned with understanding how genetic differences among individuals cause varied responses to the same drug and with the development of drug therapies to compensate for these differences.

Hairy-Cell Leukemia (HCL) – A mature B-cell lymphoid cancer which is treated with purine analogues. This hematologic malignancy is characterized by bone marrow infiltration of abnormal B cells that possess hair-like cytoplasmic projections.

PROCEDURES

1. BRAF testing is considered medical necessary when the following criteria are met:
   A. Melanoma
      1) The patient must have been diagnosed with Stage IIIC or Stage IV metastatic or unresectable melanoma; AND
      2) BRAF testing is being performed to determine drug sensitivity to an FDA-approved BRAF inhibitor (e.g., vemurafenib, dabrafenib, trametinib); AND
      3) BRAF testing has not been performed previously; AND
      4) Testing must be completed prior to initiation of therapy and be performed on formalin-fixed paraffin-embedded tissue. Testing can be performed on the primary colorectal cancer and/or the metastasis since the BRAF mutations are similar in both specimens.

      BRAF V600E tumor marker testing is not currently indicated as a companion diagnostic or for therapy selection for any other tumor types and is not covered for these conditions.

   B. Suspected or proven metastatic colorectal cancer
      1) Patients with metastatic colorectal cancer should have tumor tissue genotyped for BRAF mutations; AND
      2) Testing must be completed prior to initiation of therapy and be performed on formalin-fixed paraffin-embedded tissue. Testing can be performed on the primary colorectal cancer and/or the metastasis since the BRAF mutations are similar in both specimens.
      3) Testing will be used to identify patients that would benefit from anti-epidermal growth factor receptor (EGFR) monoclonal antibody directed therapy.

   C. Hairy Cell Leukemia
      Testing is performed to distinguish a diagnosis of hairy cell leukemia form of BRAF V6000E mutation in patients being considered for BRAF inhibitor medication (e.g., vemurafenib).

   Please see medical policy MP-061-MD- DE Molecular Tumor Markers for NSCLC for services related to non-small cell lung cancer.

   All BRAF genetic testing must be performed by an FDA-approved or CLIA-approved facility qualified to perform high complexity molecular pathology testing.

Most genomic testing should be performed once in a lifetime. Documentation in the medical record should clearly support the need for repeat testing to include the following information: recurrence of disease or change in behavior of a disease.

2. Contraindications
   There are no known contraindications for BRAF testing.

3. When BRAF testing is not covered
   BRAF testing is not covered for conditions other than those listed above because the scientific evidence has not yet been established. Noncovered conditions include and are not limited to: brain cancer/glioma, thyroid cancer, ovarian/fallopian tube/peritoneum cancers; cancer of the uterus.

4. Post-payment Audit Statement
   The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark Health Options at any time pursuant to the terms of your provider agreement.

5. Place of Service
   The place of service for BRAF testing is in the outpatient setting.

6. Genetic Counseling
   Pre- and post-test genetic counseling is required to be performed by an independent (not employed by a genetic testing lab) genetic provider prior to genetic counseling for genetic mutations. This service is necessary in order to inform persons being tested about the benefits and limitations of a specific genetic test for the specific patient. Genetic testing for mutations requires documentation of medical necessity from one of the following providers who has evaluated the patient and intends to see the person after testing has been performed for counseling:
   - Board Eligible or Board Certified Genetic Counselor
   - Advanced Genetics Nurse
   - Genetic Clinical Nurse
   - Advanced Practice Nurse in Genetics
   - Board Eligible or Board Certified Clinical Geneticist
   - A physician with experience in cancer genetics
   - A physician specializing medical oncology

GOVERNING BODIES APPROVAL

BRAF testing can be offered as laboratory-developed tests under Clinical Laboratory Improvement Amendments (CLIA) licensed laboratories. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratories offering such tests as a clinical service must meet general regulatory standards of CLIA and must be licensed by CLIA for high complexity testing.

Additional information is available at:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm

CODING REQUIREMENTS

Procedure Codes

CPT Code	Description
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)

Diagnosis Codes

ICD-10 Codes	Description
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
C21.0	Malignant neoplasm of anus, unspecified
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
C43.0	Malignant melanoma of lip
C43.10	Malignant neoplasm of unspecified eyelid, including canthus
C43.111	Malignant melanoma of right upper eyelid, including canthus (effect. 10/1/18)
C43.112	Malignant melanoma of right lower eyelid, including canthus (effect. 10/1/18)
C43.121	Malignant melanoma of left upper eyelid, including canthus (effect. 10/1/18)
C43.122	Malignant melanoma of left lower eyelid, including canthus (effect. 10/1/18)
C43.20	Malignant neoplasm of unspecified ear and external auricular canal
C43.21	Malignant neoplasm of right ear and external auricular canal
C43.22	Malignant neoplasm of left ear and external auricular canal
C43.30	Malignant neoplasm of unspecified part of face
C43.31	Malignant neoplasm of nose
C43.39	Malignant neoplasm of other parts of the face
C43.4	Malignant neoplasm of scalp and neck
C43.51	Malignant neoplasm of anal skin

C43.52	Malignant neoplasm of skin of breast
C43.59	Malignant neoplasm 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 (effect. 10/1/18)
C44.1022	Unspecified malignant neoplasm of skin of right lower eyelid, including canthus (effect. 10/1/18)
C44.1091	Unspecified malignant neoplasm of skin of left upper eyelid, including canthus (effect. 10/1/18)
C44.1092	Unspecified malignant neoplasm of skin of left lower eyelid, including canthus (effect. 10/1/18)
C44.1921	Other unspecified malignant neoplasm of skin of right upper eyelid, including canthus (effect. 10/1/18)
C44.1922	Other unspecified malignant neoplasm of skin of right lower eyelid, including canthus (effect. 10/1/18)
C44.1991	Other unspecified malignant neoplasm of skin of left upper eyelid, including canthus (effect. 10/1/18)
C44.1992	Other unspecified malignant neoplasm of skin of left lower eyelid, including canthus (effect. 10/1/18)
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
C78.4	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 other and 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
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 (effect. 10/1/18)
D03.112	Melanoma in situ of right lower eyelid, including canthus (effect. 10/1/18)
D03.121	Melanoma in situ of left upper eyelid, including canthus (effect. 10/1/18)
D03.122	Melanoma in situ of left lower eyelid, including canthus (effect. 10/1/18)
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 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

REIMBURSEMENT

Participating facilities will be reimbursed per their Highmark Health Options contract.

SUMMARY OF LITERATURE

Melanoma is a form of cancer that develops in the skin's epidermis. There are several subtypes of melanoma each having unique genetic profiles. In the early stages of melanoma, treatment may consist of surgical excision. However, in later stages, therapies such as chemotherapy and/or immunotherapy is required. It is estimated that approximately 76,380 patients will be diagnosed with and that about 10,130 patients will die from melanoma in the United States.

The BRAF gene mutation has been found in various forms of cancer. The highest incidence is in melanoma, papillary thyroid cancer, colorectal cancer, and serous ovarian cancer. While not found in high volume, the mutation has also been identified in lung cancer, glioma, ependymoma, non-Hodgkin's lymphoma, acute lymphoblastic leukemia, liver cancer, stomach cancer, and esophageal cancer.

BRAF mutations occur in approximately 50% of melanoma patients. This mutation leads to increased kinase activity resulting in extracellular signal-regulated kinase signaling and increased cellular proliferations (Puzanov and Flaherty 2010). Typically, non-chronic melanoma has a higher percentage of BRAF mutations. With the development of BRAF kinase inhibitor medications, it is important to identify patients who would gain significant clinical benefit from mutation-based targeted therapies. According to the NCCN 1.2017 guidelines, BRAF testing of primary cutaneous melanoma is not recommended unless required to guide systemic therapy.

Colorectal cancer will have 135,430 new cases diagnosed each year in the United States. At least 95,520 cases will originate in the colon and the remaining cases will originate in the rectum. BRAF mutations in patients with metastatic colon cancer do not have strong response to anti-EGFR therapies. Approximately 91% of sporadic colorectal cancers harbor BRAF mutations, whereas BRAF is almost never mutated in colorectal cancers that arise as a consequence of Lynch syndrome (Garnet and Marias, 2004).

The National Comprehensive Cancer Network (NCCN) 2016 guidelines recommend BRAF tissue testing (either primary or metastasis) at diagnosis of Stage IV disease. NCCN and the American Society of Clinical Oncology (ASCO) recommend BRAF mutation testing before initiating EGFR target therapies for patients with colorectal cancer. Furthermore, anti-EGFR therapy should be excluded from treatment of any patient with RAS or BRAF mutations.

POLICY SOURCE(S)

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National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Management of cutaneous melanoma. Accessed on July 2, 2019.

Louis DN, Ohgaki H, Wiestler HOD, et al, Who classification of tumours of the central nervous system. Revised, 4th Ed. WHO press; 2016. Accessed on July 2, 2019.

Policy History

Date	Activity
7/10/2017	Initial policy developed
12/12/2017	QI/UM committee approval
02/15/2018	Provider effective date
09/11/2018	Annual Review: Corrected typographical error in Diagnosis Code table (Attachment C) by changing C17.0 to C17.1 for malignant neoplasm of jejunum; removed the word 'Covered' from the procedure and diagnosis code tables in Attachments B & C; corrected PARP approval date in Policy History box; revised 'Related Policy Numbers' on page 1; added Hairy Cell Leukemia as a covered indication under the Procedure section; updated the diagnosis codes for HCL –C91.40, C91.41 & C91.42; updated the Reference Sources section; Removed the hyperlinks in all the references.
09/11/2018	QI/UM Committee Review Approval
11/15/2018	Provider effective date
09/10/2019	Annual Review Revision: Added reference to MP-061-MD-DE; In Section 3 removed non-small cell lung cancer and added glioma, updated Summary of Literature, Deleted procedure code G0452; deleted ICD-10 codes C43.11, C43.12, D03.11 & D03.12; added ICD-10 codes C20, C43.0, C43.11, C43.12, C43.121, C43.122, C44.1021, C44.1022, C44.1091, C44.1092, C44.1921, C44.1922, C44.1991, C44.1992, C77.0 – C77.9, C78.4 to C78.7, C78.88, C78.89, C79.00 - C79.19, C79.2, C79.31, C79.32, C79.40, C79.49, C79.51, C79.52, C79.60, C79.61, C79.62, C79.71, C79.72, C79.81, C79.82, C79.89, C79.9, D03.111, D03.112, D03.121, D03.122
09/10/2019	QI/UM Committee Review Approval
11/04/2019	Provider effective date