



CLINICAL MEDICAL POLICY	
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Responsible Department(s):	Medical Management
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Products:	Highmark Wholecare SM Medicaid
Application:	All participating hospitals and providers
Page Number(s):	1 of 12

Policy History

Date	Activity
10/01/2023	Provider Effective date
08/07/2023	PARP Approval
07/19/2023	QI/UM Committee review
07/19/2023	Annual Review: No changes to clinical criteria. Updated 'Summary of Literature' and 'Reference Sources' sections.
10/01/2022	Provider Effective date
08/08/2022	PARP Approval
07/20/2022	QI/UM Committee review
07/20/2022	Annual Review: No changes to clinical criteria. Reformatted 'Procedures' section numbering. Updated 'Summary of Literature' and 'Reference Sources' sections.
11/15/2021	Provider Effective Date
09/24/2021	PARP Approval
07/21/2021	QI/UM Committee review
07/21/2021	Annual Review: Revised general medical necessity language. Added criteria for gliomas and glioblastomas. Added ICD-10 codes C71.0-C71.9 to covered codes. Updated summary of literature and reference sections.
10/19/2020	Provider effective date
09/02/2020	PARP approval
07/15/2020	QI/UM Committee review

07/15/2020	Annual Review: Revised criteria for clarification purposes; corrected diagnosis codes descriptions for ICD-10 codes C43.10 and C43.20-C43.59; updated summary of literature, and references.
10/21/2019	Provider Effective Date
08/19/2019	PARP Approval
07/17/2019	QI/UM Committee review
07/17/2019	Annual Review: 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
07/10/2017	Initial policy developed

Disclaimer

Highmark WholecareSM 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 WholecareSM may provide coverage under the medical-surgical benefits of the Company's Medicaid products for medically necessary BRAF testing for melanoma, hairy cell leukemia 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.

(Current applicable Pennsylvania HealthChoices Agreement Section V. Program Requirements, B. Prior Authorization of Services, 1. General Prior Authorization Requirements.)

Definitions

Prior Authorization Review Panel (PARP) – A panel of representatives from within the Pennsylvania Department of Human Services who have been assigned organizational responsibility for the review, approval and denial of all PH-MCO Prior Authorization policies and procedures.

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 may be considered medical necessary for **melanoma** when ALL of the following criteria are met:
 - A. The patient has been diagnosed with Stage IIIC or Stage IV metastatic or unresectable melanoma; AND
 - B. BRAF testing is being performed to determine drug sensitivity to an FDA-approved BRAF inhibitor (e.g., vemurafenib, dabrafenib, trametinib); AND
 - C. BRAF testing has not been performed previously; AND
 - D. Testing must be completed prior to initiation of therapy;
 - E. Testing must be performed on formalin-fixed paraffin-embedded tissue.

Note: 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 considered medically necessary for these conditions.

2. BRAF testing may be considered medical necessary for **suspected or proven metastatic colorectal cancer** when ALL of the following criteria are met:
 - A. Patients with metastatic colorectal cancer should have tumor tissue genotyped for BRAF mutations; AND
 - B. Testing must be completed prior to initiation of therapy; AND
 - C. Testing must 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); AND

- D. The test should be used to determine if the patient is a candidate for anti-epidermal growth factor receptor (EGFR) monoclonal antibody directed therapy.
3. BRAF testing may be considered medical necessary for **hairy cell leukemia** when testing is performed to distinguish a diagnosis of hairy cell leukemia form of BRAF V600E mutation in patients being considered for BRAF inhibitor medication (e.g., vemurafenib).
 4. BRAF testing may be considered medically necessary when performed for individuals with **glioblastomas and gliomas** for whom the use of BRAF inhibitor regimens are being considered (e.g. vemurafenib).

Note: Additional indications and information from NCCN guidelines may be considered at the time of review.

5. Contraindications

There are no known contraindications for BRAF testing.

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 and include information regarding the recurrence of disease or change in behavior of the disease.

6. BRAF testing is considered not medically necessary for conditions other than those listed above because the scientific evidence has not yet been established. Examples include, but are not limited to:

- brain cancer/glioma
- thyroid cancer
- ovarian/fallopian tube/peritoneum cancers
- cancer of the uterus

7. Post-payment Audit Statement

The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark WholecareSM at any time pursuant to the terms of your provider agreement.

8. Place of Service

The proper place of service for BRAF testing is in the outpatient setting.

9. Related Policies

- MP-061-MD-PA Molecular Tumor Markers for Non-Small Cell Lung Cancer
- MP-065-MD-PA Molecular Markers for Fine Needle Aspirates of Thyroid Nodules
- MP-074-MD-PA Oncologic Genetic Testing Panels
- MP-126-MD-PA Pharmacogenetic Testing

10. Genetic Counseling

Pre- and post-test genetic counseling is required to be performed by an independent genetic provider (not employed by a genetic testing lab) prior to genetic testing for mutations. This service is necessary in order to inform patient being tested about the benefits and limitations of specific genetic tests. Genetic testing for mutations requires documentation of medical necessity from at least one of the following providers who has previously evaluated the patient, and intends to see the patient after genetic testing has been performed:

- 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 of appropriate expertise or other obstetrical provider specializing in the care for the indication(s) for genetic testing

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.

CMS

The Centers for Medicare and Medicaid Services (CMS) has published the following guidelines:

- Local Coverage Determination (LCD) Biomarkers for Oncology (L35396)
- Local Coverage Article (LCA) Billing and Coding: Biomarkers for Oncology (A52986)

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 are required. In 2016 it was estimated that approximately 76,380 patients will be diagnosed with and that about 10,130 patients will die from melanoma in the United States (Skin Cancer Foundation, 2015).

The BRAF gene mutation has been found in various forms of cancer. The BRAF gene is located on chromosome arm 7q34. It is composed of 18 exons, and the most common activating mutation is found in exon 15 at nucleotide position 1799, involving a transversion of thymine to adenine. More than 30 different BRAF mutations have been identified, and the mutation testing is an important tool for diagnosis, prognosis, treatment, and predicting patient outcomes in response to targeted therapy (Ziai J, Hui P, 2012).

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. 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 (Puzanov and Flaherty 2010).

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).

Hairy cell leukemia uses BRAF V600E mutation testing as it is now recognized as the causal genetic event of HCL. The reason is that mutation is somatic, present in the entire tumor clone, detectable in almost all cases at diagnosis, and stable at relapse (Falini B, Martelli MP, Tiacci E, 2016). Use of the BRAF analysis can reliably detect at the protein level in nearly all patients with HCL.

Brunangelo et al. (2016) reported that the BRAF V6000E mutation was identified as the causal genetic event of hairy cell leukemia in 2011. Among other findings, it was noted that the BRAF V600E mutation is specific for HCL. The detection of the mutation can be obtained by Sanger sequencing or other more sensitive polymerase chain reaction (PCR)-based techniques. The assays can be applied to fresh samples as well as stained air-dried, bone marrow smears and fixed-decalcified/paraffin-embedded biopsies.

In 2016, the World Health Organization (WHO) updated the classification of gliomas based on both histopathologic appearance and molecular parameters (Louis et al., 2016). The classification ranges from Grade I to IV, corresponding to the degree of malignancy, as Grade I being the least aggressive and Grade IV being most aggressive.

In a meta-analysis of pharmacogenomic substudies from eight RCTs highlights that based on the standard approach for assessing predictive markers there is insufficient evidence to conclusively demonstrate that the presence of BRAF mutation is a negative predictive biomarker of benefit from the use of anti-EGFR mAbs in RAS WT mCRC. (Rowland, 2015).

NCCN Guidelines Version 2.2023 Colon Cancer

- The panel recommends BRAF genotyping of tumor tissue (either primary or metastasis) at diagnosis of stage IV disease. Testing for BRAF V600 mutation can be performed on formalin-fixed paraffin-embedded tissues and is usually performed by PCR amplification and direct DNA sequence analysis. Allele-specific PCR, NGS, and IHC are other acceptable methods for detecting this mutation.
- As related to the workup and management of synchronous metastatic disease, the panel recommends testing for tumor KRAS/NRAS and BRAF gene status and HER2 amplifications at diagnosis. However, if the tumor is known to have a RAS or BRAF mutation, HER2 testing is not indicated, as amplification is very rare in this subset.
- In regards to the workup and management of metachronous metastatic disease a tumor analysis (metastases or original primary) for KRAS/NRAS and BRAF mutations and HER2 amplifications, as well as MSI/MMR testing if not previously done, should be performed to define whether targeted therapies can be considered among potential options.

NCCN Guidelines Version 1.2023 Hairy Cell Leukemia

- BRAF V600E mutation may serve as a reliable molecular marker to distinguish classic HCL from HCL-variant and other B-cell leukemias or lymphomas, and MAPK1 mutation analysis may be useful to distinguish HCL-variant from classic HCL in BRAF mutation-negative cases.

NCCN Guidelines Version 2.2023 Melanoma: Cutaneous

- BRAF mutation testing is recommended for patients with stage III melanoma for whom future BRAF-directed therapy may be an option.
- Mutational analysis for BRAF or multigene testing of the primary lesion is not recommended for patients with cutaneous melanoma unless required to guide adjuvant or other systemic therapy or consideration of clinical trials.
- BRAF mutations appear to be early genetic driver events in melanoma. Thus, repeat molecular testing upon recurrence or metastases is likely to be of low yield.
- 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.

NCCN Guidelines Version 1.2023 Central Nervous System Cancers

- Molecular testing of glioblastomas is encouraged by the panel, as patients with a detected driver mutation (eg, BRAF V600E mutation or NTRK fusion) may be treated with a targeted therapy on a compassionate use basis, and these tests improve diagnostic accuracy and prognostic stratification.
- Screening for BRAF fusion and/or mutation testing may be carried out as clinically indicated for gliomas.

Coding Requirements

Procedure Codes

CPT Code	Description
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600E variant(s)

Diagnosis Codes

All requests for BRAF testing services for conditions not included in this list of covered diagnosis codes must be reviewed by a Medical Director on a case-by-case basis.

ICD-10 Code	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 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 the 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 unspecified malignant neoplasm of skin of right upper eyelid, including canthus
C44.1922	Other unspecified malignant neoplasm of skin of right lower eyelid, including canthus

C44.1991	Other unspecified malignant neoplasm of skin of left upper eyelid, including canthus
C44.1992	Other unspecified malignant neoplasm of skin of left lower eyelid, including canthus
C71.0	Malignant neoplasm of cerebrum, except lobes and ventricles
C71.1	Malignant neoplasm of frontal lobe
C71.2	Malignant neoplasm of temporal lobe
C71.3	Malignant neoplasm of parietal lobe
C71.4	Malignant neoplasm of occipital lobe
C71.5	Malignant neoplasm of cerebral ventricle
C71.6	Malignant neoplasm of cerebellum
C71.7	Malignant neoplasm of brain stem
C71.8	Malignant neoplasm of overlapping sites of brain
C71.9	Malignant neoplasm of brain, unspecified
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
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 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 WholecareSM contract.

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