Effective: *12/16/2022*
Last Approved: *10/25/2022*
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Lines Of Business: *All Lines of Business*

Genetic Testing for Hereditary Breast and Ovarian Cancer Syndrome (BRAC)

PURPOSE

This policy is designed to discuss medical necessity criteria for the following tests:

- Genetic testing for BRCA1 and BRCA2 mutations in cancer-affected members.
- Genetic testing for BRCA1 and BRCA2 mutations of cancer-unaffected members in families with a strong family history of HBOC Syndrome.
- Genetic testing for PALB2, TP53, PTEN, STK11, and or CDH1 when criteria is met.

DEFINITIONS

First-degree relative: A parent, brother, sister, or child. Also called FDR.

Second-degree relative: An aunt, uncle, grandparent, grandchild, niece, nephew, or half-brother or -sister. Also called SDR.

PROCEDURE

BRCA 1 and BRCA 2 Testing

Genetic testing may be considered medically necessary for a specific BRCA1 or BRCA2 pathogenic/likely pathogenic variant (including large genomic rearrangement testing i.e. BART) when any of the following criteria are met:

- For members from a family with a known pathogenic/likely pathogenic BRCA1/BRCA2 variant; OR
- For a member with cancer or history of cancer, or unaffected members with strong family history of cancer who are at increased risk for a BRCA variant when **ANY** of the following criteria are met:

    A. For members from a family with a known pathogenic/likely pathogenic BRCA1/BRCA2 variant; OR

    B. For a member with cancer or history of cancer or for testing unaffected members with strong family history of cancer who are at increased risk for a BRCA variant when ANY of the following criteria are met:

    C. Diagnosed ≤45 years

D. Diagnosed 46-50 years with:
    i. An additional breast cancer primary at any age;
    ii. At least one first-degree relative (FDR) or second-degree relative (SDR) with breast cancer at any age;
    iii. At least one FDR or SDR with high-grade (Gleason score ≥7) prostate cancer;
E. Diagnosed ≤60 years with: Triple-negative breast cancer
F. Diagnosed at any age with, or at least one FDR or SDR with:
    i. breast cancer diagnosed ≤50 years; or
    ii. ovarian carcinoma; or
    iii. male breast cancer; or
    iv. metastatic prostate cancer; or
    v. pancreatic cancer
G. Breast cancers in any age patient and/or at least one FDR or SDR and any of the following:
    i. Ashkenazi Jewish ancestry
    ii. Personal history of ovarian carcinoma; or
    iii. Personal history of male breast cancer; or
    iv. Personal history of pancreatic cancer; or
    v. Personal history of metastatic prostate cancer; or
    vi. Personal history of high-grade prostate cancer (Gleason score ≥7) at any age with:
        a. At least one FDR or SDR with blood relative with ovarian carcinoma, pancreatic cancer, or metastatic prostate cancer at any age or breast cancer <50 years; or greater than two FDR or SDRs with breast, or prostate cancer (any grade) at any age; or Ashkenazi Jewish ancestry;
H. An individual who does not meet the other criteria but with ≥1 first- or second-degree blood relative meeting any of the above criteria. The significant limitations of interpreting test results for an unaffected individual should be discussed.
I. The member has a history of breast cancer and belongs to a population at risk for specific mutations due to ethnic background (e.g., Ashkenazi Jewish, Icelandic, Swedish, Hungarian or Dutch descent).

If a BRCA1/BRCA2 pathogenic/likely pathogenic variant is detected by tumor profiling on any tumor type, then germline BRCA1/BRCA2 analysis is considered medically necessary

In the absence of germline pathogenic/likely pathogenic variant analysis, regardless of family history, some individuals with an BRCA-related cancer may benefit from genetic testing to determine eligibility for targeted treatment.

PALB2 Gene Testing

- PALB2 gene testing may be considered when the above criteria for BRCA1/BRCA2 testing are met.

PALB2, PTEN, STK11, and or CDH1 Testing

PALB2, PTEN, STK11, and or CDH1 testing may be considered medically necessary in either of the following criteria are met:

1. Testing from a family with a known variant in these genes; OR
2. Personal history or FDR or SDRs with three or more occurrences of any of the following

- Pancreatic cancer
- Prostate cancer (Gleason >7)
- Brain tumor
- Kidney cancer
- Endometrial cancer
- Thyroid cancer
- Hamartomatous polyps of the GI tract
- Diffuse gastric cancer

TP53 Gene Testing for Li-Fraumeni Syndrome (LFS)

TP53 Gene Testing for Li-Fraumeni Syndrome may be considered medically necessary when following criteria are met:

Individual from a family with a known mutation; OR

In individuals with class LFS when all of the following are met:

- A proband with a sarcoma before 45 years of age; AND
- A first-degree relative with any cancer before 45 years of age AND
- A first-or second-degree relative with any cancer before 45 years of age or a sarcoma at any age

OR

When the following Chompret criteria are met*:*

- Proband with tumor belonging to LFS tumor spectrum (e.g., soft tissue sarcoma, osteosarcoma, brain tumor, premenopausal breast cancer, adrenocortical carcinoma, leukemia, lung bronchoalveolar cancer) before age 46 years AND
  - at least one first-or second-degree relative with LFS tumor (except breast cancer if proband has breast cancer) before age 56 years or with multiple tumors; OR
- Proband with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum and first of which occurred before age 46 years; OR
- Patient with adrenocortical carcinoma (ACC) or choroid plexus tumor, irrespective of family history

OR

In inidivdual with Early-onset breast cancer when the following criteria are met:

- NCCN recommends that in patients with breast cancer diagnosed at 35 years or younger, TP53 testing can be ordered concurrently with BRCA1/2 testing, or as a follow-up test after negative BRCA 1/2 testing. It has been estimated that among women with BRCA 1/2 negative, early-onset breast cancer, approximately 5% have a TP53 mutation.
- Note: The optimal strategy for confirming a TP53 mutation in a proband would be:

- Sequencing of the entire TP53 coding region (exons 2-11), which detects about 95% of TP53 mutations in patients with LFS.

COWDEN SYNDROME (CS)/PTEN HAMARTOMA TUMOR SYNDROME (PHTS) TESTING CRITERIA

Testing for Cowden Syndrome/PTEN harmatoma tumor syndrome (PHTS) may be considered medically necessary when any of the following are met:

- Individual from a family with a known PTEN pathogenic/likely pathogenic variant; OR
- Individual with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS); OR
- Individual meeting clinical diagnostic criteria for CS/PHTS; OR
- Individual not meeting clinical diagnostic criteria for CS/PHTS with a personal history of Adult Lhermitte-Duclos disease (cerebellar tumors); OR
- Autism spectrum disorder and macrocephaly; OR
- Two or more biopsy-proven trichilemmomas; OR
- Two or more **major criteria** (one must be macrocephaly) and
  - Breast cancer
  - Endometrial cancer
  - Follicular thyroid cancer
  - Multiple GI hamartomas or ganglioneuromas
  - Macrocephaly (megalocephaly) (i.e., ≥97%, 58 cm in adult women, 60 cm in adult men)
  - Macular pigmentation of glans penis
  - Mucocutaneous lesions
    - One biopsy-proven trichilemmoma
    - Multiple palmoplantar keratoses
    - Multifocal or extensive oral mucosal papillomatosis
    - Multiple cutaneous facial papules (often verrucous)
- Three major criteria, without macrocephaly; OR
- One major and ≥3 minor criteria; OR
- ≥4 minor criteria
  - Autism spectrum disorder
  - Colon cancer
  - ≥3 esophageal glycogenic acanthoses
  - Lipomas
  - Intellectual disability (i.e., IQ ≤75)
  - Papillary or follicular variant of papillary thyroid cancer
  - Thyroid structural lesions (e.g., adenoma, nodule(s), goiter)
  - Renal cell carcinoma
  - Single GI hamartoma or ganglioneuromatesticular lipomatosis
  - Vascular anomalies (including multiple intracranial developmental venous anomalies).

Multiple Genetic Factor Panels

Genetic testing using multi-gene panels and NGS may be considered medically necessary when any of the following are met:

- Patients who have a personal or family history suggestive of a single inherited cancer syndrome are most appropriately managed by genetic testing for that specific syndrome. When more than one gene can

explain an inherited cancer syndrome, then multi-gene testing may be more efficient and/or cost-effective.
- There may be a role for multi-gene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whose personal or family history remains suggestive of an inherited susceptibility.
- Multi-gene testing is ideally offered in the context of professional genetic expertise for pre- and post-test counseling.

Note: Testing should include only those genes that are considered medically necessary by these criteria.

Exclusions

- Genetic testing for BRCA1 and BRCA2 mutations in minors.
- BRCA and BART testing as a screening test for cancer in women in the general population.
- Testing for CHEK2 genetic abnormalities (mutations, deletions, etc.).
- Broad genetic screening with NGS for individuals who are not at increased risk.

Limitations

Once in a lifetime test.

Note: The Health Plan complies with all Medicare National Coverage Determinations (NCDs), applicable Local Coverage Determinations (LCDs), and WV Bureau for Medical Services guidelines for all therapies, items, services, and/or procedures that are covered benefits under Medicare. If the coverage criteria in this policy conflicts with any NCDs, relevant LCD, or WV BMS guidelines, the relevant document controls the application of services regardless of the version of the NCD, LCD, or WV BMS guidelines listed in the reference section.

Additional Information

Patients are considered at high risk for a BRCA variant when they meet criteria outlined in the US Preventive Services Task Force (USPSTF) BRCA-Related Cancer: Risk Assessment, Genetic Counseling, and Genetic Testing:

An individual is at increased risk for a BRCA variant as determined by any of the 5 risk stratification tools endorsed by the USPSTF listed below:

- *Ontario Family History Assessment Tool*
- *Manchester Scoring System*
- *Referral Screening Tool*
- *Pedigree Assessment Tool*
- *Family History Screen 7 (FHS-7)*

Testing of an individual without a cancer diagnosis should only be considered when an appropriate **affected** family member is unavailable for testing.

CODING

Procedure Codes:

Procedure Code	Description
81162	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis

81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81165	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81166	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81167	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81212	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
81215	BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81216	BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81217	BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; known familial varian
81308	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; known familial variant
81432	Hereditary breast cancer-hyphenrelated disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53
81433	Hereditary breast cancer-hyphenrelated disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11
0129U	Hereditary breast cancer-hyphenrelated disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53)

Diagnosis Codes:

ICD-10 Code	**Description**
C25.0 - C25.9	Malignant neoplasm of pancreas
C48.0 - C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C50.011 - C50.929	Malignant neoplasm of breast [male/female]
C56.1 - C56.9	Malignant neoplasm of the ovary [epithelial]

C61	Malignant neoplasm of prostate
D05.00 -D05.92	Carcinoma in situ, breast [invasive and ductal carcinoma in situ (DCIS) is not included]
D24.1 - D24.9	Benign neoplasm of breast [pseudo-hyphenangiomatous stromal hyperplasia (PASH) – not covered for prophylactic mastectomy] [atypical hyperplasia of lobular or ductal origin]
N60.91 - N60.99	Unspecified benign mammary dysplasia [atypical hyperplasia of lobular or ductal origin]
Z15.01	Genetic susceptibility to malignant neoplasm of breast [BRCA1 or BRCA2 mutations confirmed by molecular susceptibility testing for breast cancer] [genetic mutation in the TP53 or PTEN genes (Li-hyphenFraumeni syndrome, Cowden syndrome, and Bannayan-hyphenRiley-hyphenRuvalcaba syndrome)]
Z15.02	Genetic susceptibility to malignant neoplasm of ovary [BRCA1 or BRCA2 mutations confirmed by molecular susceptibility testing for ovarian cancer]
Z40.01	Encounter for prophylactic removal of breast
Z40.02	Encounter for prophylactic removal of ovary(s)
Z80.0	Family history of malignant neoplasm of digestive organs [pancreas]
Z80.3	Family history of malignant neoplasm of breast
Z80.41	Family history of malignant neoplasm of ovary [epithelial]
Z80.42	Family history of malignant neoplasm of prostate
Z84.81	Family history of carrier of genetic disease
Z85.07	Personal history of malignant neoplasm of pancreas

REFERENCES

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The American College of Obstetricians and Gynecologists (ACOG). Committee Opinion Number 739: Hereditary Cancer Syndromes and Risk Assessment. December 2019. Accessed September 8, 2022. https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2019/12/hereditary-cancer-syndromes-and-risk-assessment

POLICY HISTORY

Date	Description
9/28/ 2022	Annual Review: Added policy purpose section. Changed "Medical Policy Guidance" section to "Procedure". Reformatted criteria for clarity. Renamed 'Recommendations" to "Additional Information". Added note regarding NCDs/LCDs. Added the following sections: Coding (CPT and diagnosis), References, Post-Payment Audit Statement, and Disclaimer.

POST-PAYMENT AUDIT STATEMENT:

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

DISCLAIMER:

This policy is intended to serve as a guideline only and does not constitute medical advice, any guarantee of payment, plan pre-authorization, an explanation of benefits, or a contract. This policy is intended to address medical necessity guidelines that are suitable for most individuals. Each individual's unique clinical situation may warrant individual consideration based on medical records. Individual claims may be affected by other factors, including but not necessarily limited to state and federal laws and regulations, legislative mandates, provider contract terms, and THP's professional judgment. Reimbursement for any services shall be subject to member benefits and eligibility on the date of service, medical necessity, adherence to plan policies and procedures, claims editing logic, provider contractual agreement, and applicable referral, authorization, notification, and utilization management guidelines. Unless otherwise noted within the policy, THP's policies apply to both participating and non-participating providers and facilities. THP reserves the right to review and revise these policies periodically as it deems necessary in its discretion, and it is subject to change or termination at any time by THP. THP has full and final discretionary authority for its interpretation and application. Accordingly, THP may use reasonable discretion in interpreting and applying this policy to health care services provided in any particular case.

All revision dates: 10/25/2022, 11/3/2020