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Genetic Testing for Hereditary Cancers: Breast, Ovarian, and Pancreatic

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.

Close blood relative: First-, second-, and third-degree relatives on the same side of the family.

PROCEDURE

Genetic Testing for Individuals with a Personal History of Breast Cancer- BRCA1, BRCA2, CDH1, PALB2, PTEN, and TP53

Genetic testing for susceptibility to breast cancer may be considered medically necessary for any of the following indications:

- When an individual develops breast cancer at age 50 or younger; or
- When an individual develops breast cancer at any age and any of the following are true:

    - Triple-negative breast cancer, or
    - Multiple primary breast cancers, or
    - Lobular breast cancer with a personal or family history of diffuse gastric cancer, or
    - Male breast cancer, or
    - Ashkenazi Jewish ancestry, or
    - One of more close blood relative with any of the following:
        - Breast cancer at age ≤50 years, or
        - Male breast cancer, or
        - Ovarian cancer, or
        - Pancreatic cancer, or
        - Metastatic prostate cancer, or prostate cancer that is classified as high- or very-hish-risk; or
    - Three or more total diagnosis of breast cancer in the individual and/or among their close blood relatives; or
    - Two or more close blood relative with either breast cancer or prostate cancer; or
- When an individual develops breast cancer at any age and genetic testing is needed to aid in treatment decisions in either of the following instances:
    - The use of PARP inhibitors metastatic breast cancer, or
    - The use of olaparib for high-risk, HER2-negative breast cancer.

Genetic Testing for Individuals with a Family History of Breast Cancer

Genetic testing in unaffected individuals with a family history of breast cancer may be considered medically necessary in the following situations:

- An affected individual (not meeting testing criteria listed above) or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).
    - If the affected relative has pancreatic cancer or prostate cancer only first-degree relatives should be offered testing unless indicated based on additional family history.
- An affected or unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a BRCA1/2 pathogenic variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, CanRisk).

Genetic Testing for Ovarian Cancer Susceptibilit7

Genetic testing for susceptibility to ovarian cancer may be considered medically necessary in either of

the following situations:

- Any personal history of epithelial ovarian cancer at any age (including fallopian tube and peritoneal cancer);
- An individual with a family history of ovarian cancer in either of the following scenarios:
    - When an unaffected individual with a first- or second-degree blood relative with epithelial ovarian cancer at any age (including fallopian tube and peritoneal cancer); or
    - An unaffected individual who does not meet the above criteria, but has a probability of >5% of having a BRCA 1 or 2 pathogenic variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, CanRisk).

Genetic Testing for Pancreatic Cancer Susceptibility

Genetic testing for susceptibility to pancreatic cancer may be considered medically necessary for any of the following indications:

- Individuals diagnosed with exocrine pancreatic cancer; or
- First-degree relatives of individuals diagnosed with exocrine pancreatic cancer

Genetic Testing for Li-Fraumeni Syndrome (LFS)

Genetic testing for Li-Fraumeni Syndrome may be considered medically necessary when following criteria are met:

Individual from a family with a known TP53 P/LP variant; OR

In individuals with classic Li-Fraumeni syndrome (LFS) when all of the following are met:

- When an individual is diagnosed with a sarcoma <45 years of age; AND
- A first-degree relative diagnosed at age <45 with any cancer; 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*:*

- Individual with a tumor from LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma), before 46 years of age, AND at least one first- or second-degree relative with any of the aforementioned cancers (other than breast cancer if the proband has breast cancer) before the age of 56 years or with multiple primaries at any age; OR
- Individual with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum with the initial cancer occurring before the age of 46 years; OR
- Individual with adrenocortical carcinoma, or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype, at any age of onset, regardless

of family history; OR

- Breast cancer before 31 years of age.

OR

Individuals with pediatric hypodiploid acute lymphoblastic leukemia; OR

Affected individual with P/LP variant identified on tumor genomic testing that may have implications if also identified on germline testing.

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 P/LP 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 (see below); OR
- Individual not meeting clinical diagnostic criteria for CS/PHTS with a personal history of any of the following:
    - 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); OR
    - Three major criteria, without macrocephaly; OR
    - One major and ≥3 minor criteria; OR
    - ≥4 minor criteria;
- OR
- At-risk individual with a relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed
    - The at-risk individual must have the following:
        - Any one major criterion; OR
        - Two minor criteria;
- OR
- PTEN P/LP variant detected by tumor genomic testing on any tumor type in the absence of germline analysis.

Clinical Diagnostic Criteria for Cownden/PTEN Harmatoma Tumor Syndrome

- Operational diagnosis in an individual (either of the following):
    - Three or more major criteria, but one must include macrocephaly, Lhermitte-Duclos

disease, or GI hamartomas; OR
    - Two major and three minor criteria.

- Operational diagnosis in a family where one individual meets revised PTEN hamartoma tumor syndrome clinical diagnostic criteria or has a PTEN P/LP variant:
    - Any two major criteria with or without minor criteria; OR
    - One major and two minor criteria; OR
    - Three minor criteria.

- Major Criteria:
    - Breast cancer
    - Endometrial cancer
    - Follicular thyroid cancer
    - Multiple GI hamartomas or ganglioneuromas
    - Macrocephaly (megalocephaly) (ie, ≥97%, 58 cm in adult female, 60 cm in adult male)
    - 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)

- Minor Criteria
    - Autism spectrum disorder
    - Colon cancer
    - ≥3 esophageal glycogenic acanthoses
    - Lipomas
    - Intellectual disability (ie, IQ ≤75)
    - Papillary or follicular variant of papillary thyroid cancer
    - Thyroid structural lesions (eg, adenoma, nodule[s], goiter)
    - Renal cell carcinoma
    - Single GI hamartoma or ganglioneuroma
    - Testicular 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

THP follows the NCCN Guidelines for Breast, Ovarian, and/or Pancreatic Cancer Genetic Assessment. Please refer to their website for additional information.

Prior to genetic testing, the following should be taken into consideration:

- The probability of P/LP variant detection associated with these criteria will vary based on family structure, which includes size of the family, age of the family members, early death, adoption, and number of male and female relatives. Individuals with unknown or limited family history/structure, such as fewer than 2 female first- or second-degree relatives having lived beyond age 45 in either lineage, may have an underestimated probability of familial P/LP variant detection. The estimated likelihood of P/LP variant detection may be low in families with a large number of unaffected and/or male relatives.
- Patients who have received an allogeneic bone marrow transplant or with active or recent hematologic malignancies should not have molecular genetic testing via blood, saliva, or

buccal samples (due to unreliable test results from contamination by donor DNA) until other technologies are available. If available, DNA should be extracted from a fibroblast culture. If this source of DNA is not possible, buccal samples can be considered, subject to the risk of donor DNA contamination or malignant cells from the hematologic malignancy.

- If more than one family member is affected with cancers highly associated with a particular inherited cancer susceptibility syndrome, consider initial testing of a family member with youngest age at diagnosis, bilateral disease, multiple primary cancers, or other cancers associated with the syndrome, or most closely related to the proband/patient. If there are no available family members with cancer that is a cardinal feature of the syndrome in question, consider testing first- or second-degree family members affected with other cancers thought to be related to the gene in question (eg, prostate or pancreas with BRCA1/2).
- Testing for unaffected family members when no affected member is available should be considered. Significant limitations of interpreting test results should be discussed.
- In children <18 y, genetic testing is generally not recommended when results would not impact medical management.
- LP variants are usually clinically managed similarly to pathogenic variants, while patients with variants of uncertain significance (VUS) and likely benign variants should be managed based on the cancers present in the family.

CODING

Procedure Codes:

Procedure Code	Description
81162	BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., 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) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81165	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81166	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81167	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81212	BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants

81215	BRCA1 (breast cancer 1) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
81216	BRCA2 (breast cancer 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81217	BRCA2 (breast cancer 2) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
81307	PALB2 (partner and localizer of BRCA2) (e.g., breast and pancreatic cancer) gene analysis; full gene sequence
81308	PALB2 (partner and localizer of BRCA2) (e.g., breast and pancreatic cancer) gene analysis; known familial variant
81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81322	PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
81323	PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant
81351	TP53 (tumor protein 53) (e.g., Li-Fraumeni syndrome) gene analysis; full gene sequence
81352	TP53 (tumor protein 53) (e.g., Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (eg, 4 oncology)
81353	TP53 (tumor protein 53) (e.g., Li-Fraumeni syndrome) gene analysis; known familial variant
81432	Hereditary breast cancer-related disorders (e.g., 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-related disorders (e.g., 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-related disorders (e.g., 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

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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.
8/23/2023	Annual Review: Added Pancreatic to the title. Added definition for close family relatives. Reformatted and updated all criteria to follow NCCN criteria, and included criteria for pancreatic cancer. Updated references and links. Revised Additional Information section. Corrected typos. Added CPT codes 81307, 81321, 81322, 81323, 81351, 81532, and 81353.

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

9/15/2023, 10/25/2022, 11/3/2020