Genetic Testing for Hereditary Breast and Ovarian Cancer Syndrome

Medical Policy Guidance:

RECOMMENDATION

- 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.

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.

INCLUSIONS

Breast and Ovarian Cancer

Inclusion Criteria for BRAC 1/2 Testing

Genetic testing is considered medically necessary for a specific BRCA1 or BRCA2 pathogenic/likely pathogenic variant (including large genomic rearrangement testing i.e. BART):

1. For members from a family with a known pathogenic/likely pathogenic BRCA1/BRCA2 variant; **OR**
2. 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:

   A. Diagnosed ≤45 years

B. Diagnosed 46-50 years with:
   - An additional breast cancer primary at any age;
   - ≥1 close blood relative with breast cancer at any age;
   - ≥1 close blood relative with high-grade (Gleason score ≥7) prostate cancer;

C. Diagnosed ≤60 years with: Triple-negative breast cancer

D. Diagnosed at any age with: ≥1 close blood relative with:
   - Breast cancer diagnosed ≤50 years; or
   - Ovarian carcinoma; or
   - Male breast cancer; or
   - Metastatic prostate cancer; or
   - Pancreatic cancer

E. Breast cancers in any age patient and/or Close (1st or 2nd degree) relatives and any of the following:
   - Ashkenazi Jewish ancestry
   - Personal history of ovarian carcinoma; or
   - Personal history of male breast cancer; or
   - Personal history of pancreatic cancer; or
   - Personal history of metastatic prostate cancer; or
   - Personal history of high-grade prostate cancer (Gleason score ≥7) at any age with:
     - ≥1 close blood relative with ovarian carcinoma, pancreatic cancer, or metastatic prostate cancer at any age or breast cancer <50 years; or Greater than 2 close blood relatives with breast, or prostate cancer (any grade) at any age; or Ashkenazi Jewish ancestry;

F. 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.

G. 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 BRCA1/2 pathogenic/likely pathogenic variant is detected by tumor profiling on any tumor type, then germline BRCA1/2 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 when criteria for BRCA 1/2 testing are met.

PALB2, PTEN, STK11, and or CDH1 Testing

1. Testing from a family with a known variant in these genes, OR;
2. Personal history or close relatives 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

When following criteria are met:

Individual from a family with a known mutation or

Classic LFS:

- 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

Chompret Criteria:

- 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

Early-Onset Breast Cancer:

- 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.
- 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

- 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 criteriae 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 should include only those genes that are considered medically necessary by these criteria.

- 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 posttest counseling.

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.

DEFINITION

Close Relative – first or second degree relative