Breast Cancer Genetic Testing - Single Service

Clinical Guidelines for Medical Necessity Review

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Important Notices

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Guideline Information:

Specialty Area: Laboratory Tests
Guideline Name: Breast Cancer Genetic Testing

Literature review current through: 12/8/2023
Document last updated: 12/8/2023
Type: [**X**] Adult (18+ yo) | [_] Pediatric (0-17yo)

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Medical Necessity Criteria

Service: Breast Cancer Genetic Testing

General Guidelines

- **Units, Frequency, & Duration:** Once
- **Criteria for Subsequent Requests:** Expansion in scope, specificity, and availability of genetic testing may indicate the need for additional testing.
- **Recommended Clinical Approach:** Genetic testing for hereditary breast cancer (eg, *BRCA1/BRCA2, PTEN, PIK3CA*) is a continually evolving technology; however, medical societies, particularly the National Comprehensive Cancer Network (NCCN) and the American Society of Breast Surgeons have published established guidelines for use. Single- or multi-gene panels are available for use following risk assessment with established clinical tools and certified genetic counselor guidance.[1] This testing is performed on the individual and not the individual's tumor.
  Gene expression profiling tests may be performed on confirmed breast cancer cells after surgery or biopsy to look for patterns in different genes. This is usually done in order to tailor the treatment, particularly chemotherapy, of an individual with breast cancer, as well as to predict the chance of recurrence.[2]
- **Exclusions:** None

Medical Necessity Criteria

Indications

➔ **Breast cancer genetic testing** is considered appropriate if **ANY** of the following is **TRUE**:

- ◆ **Genetic testing for hereditary breast cancer** (single or multi-gene) may be appropriate for **ANY** of the following:
  - **Personal history** of breast cancer (including ductal carcinoma in situ [DCIS]) and **ANY** of the following[3-7]:
    - Age 50 or younger; **OR**
    - Any age with **ANY** of the following:
      - ◆ Treatment indications, including **ANY** of the following:

        - Using poly-ADP ribose polymerase (PARP) inhibitors for metastatic breast cancer to aid in systemic treatment decisions; **OR**
        - To aid in adjuvant treatment decisions with olabarib for high-risk, HER-2 negative breast cancer; **OR**
    - The individual has pathology/histology of **ANY** of the following:
        - Triple-negative breast cancer; **OR**
        - Multiple primary breast cancers (synchronous or metachronous); **OR**
        - Lobular breast cancer with personal or family history of diffuse gastric cancer; **OR**
    - Male breast cancer; **OR**
    - Ashkenazi Jewish ancestry; **OR**
    - Family history of **ANY** of the following:
        - **One or more** close blood relatives[3]* with **ANY** of the following:
            - Breast cancer at age 50 or younger; **OR**
            - Male breast cancer; **OR**
            - Ovarian cancer; **OR**
            - Pancreatic cancer; **OR**
            - Prostate cancer with metastatic or high or very high-risk group; **OR**
        - At least three diagnoses of breast/and or prostate cancer (any grade) on the same side of the family, including the patient with breast cancer; **OR**
- **Family history** of breast cancer with **ANY** of the following:
    - Individuals affected with breast cancer (not meeting testing criteria listed above) with a first or second degree blood relative meeting any of the criteria listed above; **OR**
    - Individuals unaffected with breast cancer 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); **OR**
    - Individuals affected or unaffected with breast cancer who otherwise do not meet the criteria above but have a probability of greater than 5% of a BRCA1/2P/LP variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, CanRisk); **OR**

- **Gene expression profiling tests** may be appropriate for **ALL** of the following[2,6]:
  - HER2 negative breast tumor; **AND**
  - Hormone receptor-positive breast tumor; **AND**
  - Breast tumor greater than 0.5 cm in size; **AND**
  - The individual meets the criteria for adjuvant therapy (no significant comorbidities or advanced age); **AND**
  - **EITHER** of the following:
    - Node-negative or with one to three positive nodes (81522, 81521, 81523, 81529); **OR**
    - Node-negative or axillary-node micrometastasis 2.0 mm or less (81520); **OR**
- **Gene expression profiling tests for ductal carcinoma in-situ (DCIS)** (0045U) may be appropriate for **ALL** of the following[2,8]:
  - Either excisional or core biopsy pathology demonstrates ductal carcinoma in situ of the breast; **AND**
  - No pathological evidence of invasive disease; **AND**
  - FFPE specimen has at least 0.5 mm of DCIS length; **AND**
  - The patient is considering, and is a candidate for, **ANY** of the following:
    - Breast-conserving surgery; **OR**
    - Breast-conserving surgery with adjuvant radiation therapy

*__Close blood relatives__ include the following: First degree-Child, full-sibling, parent, Second degree-Aunt, uncle, grandchild, grandparent, nephew, niece, half-sibling, Third degree-First cousin, great-aunt, great-uncle, great-grandchild, great-grandparent, half-aunt, half uncle (NCCN defines close blood relative as a first, second or third degree relative on the same side of the family)[3]

Non-Indications

- **Breast cancer genetic testing** is **NOT** considered appropriate if **ANY** of the following is **TRUE**:
  - **Genetic testing for hereditary breast cancer** (single or multi-gene) is **NOT** considered appropriate for women whose personal or family history/ancestry is not associated with potentially harmful *BRCA1/2* gene mutations[9]; **OR**
  - **Direct-to-consumer testing** is **NOT** considered appropriate for any indication[6]; **OR**
  - **Gene expression profiling** testing is **NOT** considered appropriate for **ANY** of the following[10]:

- Metastatic or locally advanced breast cancer with four or more positive nodes; **OR**
- HER2 positive breast cancer; **OR**
- Triple-negative breast cancer; **OR**
- Gene expression profiling tests for ductal carcinoma in-situ (DCIS) are **NOT** considered appropriate when mastectomy is planned

Level of Care Criteria

Outpatient

Procedure Codes (HCPCS/CPT)

HCPCS/CPT Code	Code Description
81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (ie, detection of large gene rearrangements)
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 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
81215	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81216	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81217	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81307	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; full gene sequence
81308	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; known familial variant
81309	PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha) (eg, colorectal and breast cancer) gene analysis, targeted sequence analysis (eg, exons 7, 9, 20)
81432	Hereditary breast cancer-related 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-related 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
81519	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score
81520	Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score
81521	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81522	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
81523	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
0045U	Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score

Medical Evidence

National and Professional Organizations

The National Comprehensive Cancer Network (NCCN) updated established guidelines in 2024 for genetic/familial high risk assessment. NCCN recommends pre- and post-genetic testing counseling and selection of appropriate testing with a genetic counselor, clinical geneticist, oncologist, surgeon, oncology nurse or other health professional experienced in cancer genetics. Family history assessment is a critical component of the genetic evaluation.

The Centers for Disease Control (CDC) (2023) has published information regarding genetic testing for hereditary breast and ovarian cancer and stresses that having a strong family history of breast cancer does not mean that an individual will have an inherited mutation. They state that most women identified as being at higher risk for *BRCA1/2* mutations per family history do not have the mutation. Individuals found to have the mutation may not have a strong family history of breast cancer.

Manahan et al. (2019) published a consensus guideline for the American Society of Breast Surgeons with the following recommendations:

- Medical professionals knowledgeable in genetic testing (breast surgeons, genetic counselors) recommended to provide patient education, counseling, and recommendations for testing. They state that there is a lack of consensus among experts regarding which genes should be tested in various clinical scenarios.
- The recommendation is made that all patients with a personal history of breast cancer should be offered testing, including *BRCA1/2* and *PALB2* mutations. They state that treatment recommendations could be enhanced by testing.
- Patients who have previously had genetic testing may benefit from updated testing, particularly if performed before 2014, as *PALB2* testing was not in use at that time.
- Patients who meet NCCN guidelines who do not have a personal history of breast cancer should be tested unless an affected relative is available for testing, which is preferred.

- When variants of uncertain significance are found, no clinical action is needed. Patients should be managed based on risk factors and not these inconclusive results.

Hampel et al. (2014) recommend referral for breast cancer genetic testing consultation for females and males, and recommendations generally mirror those of the NCCN.

The US Preventive Services Task Force (USPSTF) published a 2019 recommendation recommending against routine risk assessment, genetic counseling, or genetic testing for women whose personal or family history/ancestry is not associated with *BRCA1/2* mutations (D recommendation, benefits small to moderate)

References

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Clinical Guideline Revision History/Information

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