05-82000-30

Original Effective Date: 10/15/01

Reviewed: 10/24/24

Revised: 01/01/25

Subject: Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions	Related Guidelines
Other	References	Updates			

DESCRIPTION:

Several genetic syndromes with an autosomal dominant pattern of inheritance that feature breast cancer have been identified. Of these, hereditary breast and ovarian cancer (HBOC) and some cases of hereditary site-specific breast cancer have in common causative mutations in BRCA (breast cancer susceptibility) genes. Families suspected of having HBOC syndrome are characterized by an increased susceptibility to breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, and ovarian cancer at any age as well as cancer of the fallopian tube and primary peritoneal cancer. Other cancers, such as prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer, occur more frequently in HBOC families. Hereditary site-specific breast cancer families are characterized by early-onset breast cancer with or without male cases, but without ovarian cancer.

Germline variants in the BRCA1 and BRCA2 genes are responsible for the cancer susceptibility in most HBOC families, especially if ovarian cancer or male breast cancer are features. However, in site-specific breast cancer, BRCA variants are responsible for only a proportion of affected families. BRCA gene variants are inherited in an autosomal dominant fashion through either the maternal or paternal lineage. It is possible to test for abnormalities in BRCA1 and BRCA2 genes to identify the specific variant in cancer cases, and to identify family members at increased cancer risk. Family members without existing cancer who are found to have BRCA variants can consider preventive interventions for reducing risk and mortality.

The PALB2 gene (partner and localizer of BRCA2) encodes for a protein and the PALB2 protein assists BRCA2 in DNA repair and tumor suppression. Heterozygous pathogenic PALB2 variants increase the risk

of developing breast and pancreatic cancers and affected individuals also carry a risk of other cancers including leukemia. In women with a family history of breast cancer, the prevalence of pathogenic PALB2 variants ranges between 0.9% and 3.9%,or substantially higher than in an unselected general population. Depending on population prevalence, PALB2 may be responsible for as much as 2.4% of hereditary breast cancers.

Summary and Analysis of Evidence: Genetic testing for a BRCA1 or BRCA2 variant for patients who have cancer or a personal or family cancer history and meet criteria suggesting a risk of hereditary breast and ovarian cancer (HBOC) syndrome, the evidence includes a TEC Assessment and studies of variant prevalence and cancer risk. The accuracy of variant testing has been shown to be high. Studies of lifetime risk of cancer for carriers of a BRCA variant have shown a risk as high as 85%. Knowledge of BRCA variant status in individuals at risk of a BRCA variant may impact health care decisions to reduce risk, including intensive surveillance, chemoprevention, and/or prophylactic intervention. In individuals with BRCA1 or BRCA2 variants, prophylactic mastectomy and oophorectomy have been found to significantly increase disease-specific survival and OS. Knowledge of BRCA variant status in individuals diagnosed with breast cancer may impact treatment decisions. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. For patients with other high-risk cancers (eg, cancers of the fallopian tube, pancreas, prostate) who are tested for a BRCA1 or BRCA2 variant, the evidence includes studies of variant prevalence and cancer risk. Knowledge of BRCA variant status in individuals with other high-risk cancers can inform decisions regarding genetic counseling, chemotherapy, and enrollment in clinical trials. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. Patients with a risk of HBOC syndrome who are tested for a PALB2 variant, the evidence includes studies of clinical validity and studies of breast cancer risk, including a meta-analysis. Evidence supporting clinical validity was obtained from numerous studies reporting relative risks (RRs) or odds ratios (ORs). Study designs included family segregation, kin-cohort, family-based case-control, and population-based case control. The number of pathogenic variants identified in studies varied from 1 (founder mutations) to 48. The relative risk for breast cancer associated with a PALB2 variant ranged from 2.3 to 13.4, with the 2 family-based studies reporting the lowest values. Evidence of preventive interventions in women with PALB2 variants is indirect, relying on studies of high-risk women and BRCA carriers. These interventions include screening with magnetic resonance imaging, chemoprevention, and risk-reducing mastectomy. Given the penetrance of PALB2 variants, the outcomes following bilateral and contralateral risk-reducing mastectomy examined in women with a family history consistent with hereditary breast cancer (including BRCA1 and BRCA2 carriers) can be applied to women with PALB2 variants, with the benefit-to-risk balance affected by penetrance. In women at high-risk of hereditary breast cancer who would consider risk-reducing interventions, identifying a PALB2 variant provides a more precise estimated risk of developing breast cancer compared with family history alone and can offer women a more accurate understanding of benefits and potential harms of any intervention. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. The use of genetic testing for BRCA1, BRCA2, or PALB2 variants for identifying hereditary breast ovarian cancer syndrome has limited to no clinical utility in minors. There is no change in management for minors as a result of knowledge of the presence or absence of a deleterious variant. In addition, there are potential harms related to stigmatization and discrimination.

POSITION STATEMENT:

NOTE: Coverage for genetic testing, screening, and counseling are applicable only under those contracts that include benefits for genetic testing, preventive health services, screening services, and medical counseling. Coverage may be governed by state or federal mandates.

Genetic testing for BRCA1, BRCA2, and PALB2 variants **meets the definition of medical necessity** for cancer-affected members who meet **ONE** or more of the following criteria:

1. Member with any close blood relative* with a known BRCA1, BRCA2, or PALB2 pathogenic/likely pathogenic variant.
2. Member meeting the criteria below but with previous limited testing (e.g., single gene and/or absent deletion duplication analysis).
3. Personal history of breast cancer and **ONE** or more of the following:
    - Diagnosed at age ≤45 years;
    - Diagnosed age 46-50 years with:
        - An additional breast cancer primary (bilateral disease or two or more clearly separate ipsilateral primary tumors diagnosed either synchronously or asynchronously) at any age; or
        - ≥1 close blood relative* with breast, ovarian, pancreatic, or prostate cancer at any age; or
        - An unknown or limited family history.
    - Diagnosed age ≤ 60 years with a triple-negative breast cancer;
    - Diagnosed at any age with:
        - ≥1 close blood relative* with:
            - Breast cancer diagnosed ≤50 years; or
            - Ovarian carcinoma (includes fallopian tube & primary peritoneal cancers); or
            - Metastatic, intraductal/cribiform prostate cancer, or high-risk or very-high-risk group** prostate cancer; or
            - Pancreatic cancer.
        - ≥3 total diagnoses of breast cancer in member and/or close blood relative*
        - Ashkenazi Jewish ancestry.
    - Diagnosed at any age with male breast cancer.
4. Personal history of epithelial ovarian carcinoma (including fallopian tube cancer or peritoneal cancer) at any age.
5. Personal history of exocrine pancreatic cancer at any age.
6. Personal history of metastatic or intraductal/cribiform histology prostate cancer at any age; or high-risk group or very-high-risk group** prostate cancer at any age.

7. Personal history of prostate cancer at any age with:
    - ≥1 close blood relative* with ovarian carcinoma, pancreatic cancer, or metastatic, or intraductal/cribiform prostate cancer at any age, or breast cancer ≤50 years; or
    - ≥2 close blood relatives* with breast or prostate cancer (any grade) at any age; or
    - Ashkenazi Jewish ancestry.
8. Personal history of a BRCA1, BRCA2, or PALB2 pathogenic/likely pathogenic variant identified on tumor genomic testing that has clinical implications if also identified in the germline.

Genetic testing for BRCA1, BRCA2, and PALB2 variants of cancer-unaffected members and members with cancer but not meeting the above criteria (including members with cancers unrelated to hereditary breast ovarian cancer syndrome) **meets the definition of medical necessity** under any **ONE** of the following circumstances:

- A member with or without cancer and not meeting the above criteria but who has a 1st- or 2nd-degree blood relative* meeting any criterion listed above for Members With Cancer.
- A member with any type of cancer (cancer related to hereditary breast ovarian cancer syndrome but not meeting above criteria, or cancer unrelated to hereditary breast ovarian cancer syndrome) or unaffected member who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2 or PALB2* pathogenic variant based on prior probability models (*e.g.*, Tyrer-Cuzick, BRCAPro, Penn ll).

*****Close blood relatives include 1st-, 2nd-, and 3rd- degree relatives on the same side of the family (maternal or paternal): **1st-degree** relatives: parents, siblings, and children; **2nd-degree** relatives: grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings; **3rd-degree** relatives: great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.

****High-risk group**: no very-high-risk features and are T3a (American Joint Committee on Cancer staging T3a=tumor has extended outside of the prostate but has not spread to the seminal vesicles); OR Grade Group 4 or 5; OR prostate specific antigen of 20 ng/ml or greater. Very-high-risk group: T3b-T4 (tumor invades seminal vesicle(s); or tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall); OR Primary Gleason Pattern 5; OR 2 or 3 high-risk features; OR greater than 4 cores with Grade Group 4 or 5.

BRACAnalysis® Rearrangement Test (BART™) **meets the definition of medical necessity** for individuals that meet the BRCA testing criteria listed above.

BRACAnalysis Rearrangement Test (BART) is considered **experimental or investigational** for all other indications including screening in the general population. There is a lack of clinical data to permit conclusions on the clinical management of the patient and net health outcomes.

Genetic testing for BRCA1 and BRCA2 variants in cancer-affected members or of cancer-unaffected members with a family history of cancer when criteria above are not met is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes.

Testing for PALB2 variants in members who do not meet the criteria outlined above is considered **experimental or investigational**. The evidence is insufficient to determine the effects on health outcomes.

Genetic testing in minors for BRCA1, BRCA2, and PALB2 variants is considered **experimental or investigational**. There is no change in management for minors as a result of knowledge of the presence or absence of a deleterious variant. In addition, there are potential harms related to stigmatization and discrimination.

BILLING/CODING INFORMATION:

CPT Coding:

81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., 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) (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 (ie, 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 (ie, detection of large gene rearrangements)
81167	BRCA2 (BRCA2, DNA repair associated) (e.g., 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) (e.g., hereditary breast and ovarian cancer) gene analysis;185delAG, 5385insC, 6174delT variants
81215	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
81216	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) geneanalysis; full sequence analysis
81217	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) geneanalysis; 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
96041	Medical genetics and genetic counseling services, each 30 minutes of total time provided by the genetic counselor on the date of the encounter

HCPCS Coding:

S0265	Genetic counseling, under physician supervision, each 15 minutes

REIMBURSEMENT INFORMATION:

None applicable

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage products: The following were reviewed on the last guideline reviewed date: Local Coverage Determination (LCD) BRCA1 and BRCA2 Genetic Testing (L36499); Billing and Coding Article: BRCA1 and BRCA2 Genetic Testing (A57449) located at fcso.com.

DEFINITIONS:

Triple-negative breast cancer: describes breast cancer cells that do not have estrogen receptors, progesterone receptors, or large amounts of HER2/neu protein. Also called ER-negative PR-negative HER2/neu-negative and ER-PR-HER2/neu-.

RELATED GUIDELINES:

Genetic Testing, 05-82000-28
Magnetic Resonance Imaging of the Breast, 04-70540-09
Preventive Services, 01-99385-03
Prophylactic Mastectomy, 02-12000-15

OTHER:

None applicable

REFERENCES:

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3. American College of Obstetricians and Gynecologists (ACOG), Routine Screening for Hereditary Breast and Ovarian Cancer Recommended; accessed at acog.org.
4. The American Society of Breast Surgeons, Position Statement on BRCA Genetic Testing for Patients With and Without Breast Cancer, 09/2012, accessed at breastsurgeons.org.

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6. Bedrosian I, Somerfield MR, et al. Germline Testing in Patients With Breast Cancer: ASCO-Society of Surgical Oncology Guideline. J Clin Oncol. 2024 Feb 10;42(5):584-604.

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8. Blue Cross Blue Shield Association Evidence Positioning System®. 2.04.02 Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2); 09/24.

9. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). BRCA1 and BRCA2 testing to determine the risk of breast and ovarian cancer. TEC Assessments. 1997;Volume 12:Tab 4.

10. First Coast Service Options, Inc. (FCSO) Billing and Coding Article: BRCA1 and BRCA2 Genetic Testing (A57449); located at fcso.com.

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12. Hirst JE, Gard GB, McIllroy K, et al, High Rates of Occult Fallopian Tube Cancer Diagnosed at Prophylactic Bilateral Salpingo-Oophorectomy, Int J Gynecol Cancer 2009; 19(5): 826-9.

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14. Kristeleit RS, Oaknin A, et al. Antitumor activity of the poly(ADP-ribose) polymerase inhibitor rucaparib as monotherapy in patients with platinum-sensitive, relapsed, BRCA -mutated, high-grade ovarian cancer, and an update on safety. Int J Gynecol Cancer. Nov 2019; 29(9): 1396-1404. PMID: 31685558.

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16. National Cancer Institute (NCI), NCI Fact Sheet- BRCA1 and BRCA2: Cancer Risk and Genetic Testing, last reviewed: 01/22/14; accessed at cancer.gov.

17. National Comprehensive Cancer Network, (NCCN) Clinical Practice Guidelines in Oncology, Genetic/Familial High-Risk Assessment: Breast and Ovarian; accessed at nccn.org.

18. National Institute for Health and Care Excellence. Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy.[TA598] August 2019; accessed at nice.org.uk.

19. Peshkin BN, Isaacs C. Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes. In: UpToDate,Chagpar AB, Goff B, Burstein HJ, Vora SR (eds), UpToDate, Waltham, MA; accessed December 2020 at uptodate.com.

20. Robson ME, Tung N, et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. Ann Oncol. Apr 01 2019; 30(4): 558-566.

21. Tung N, Ricker C, et al. Selection of Germline Genetic Testing Panels in Patients With Cancer: ASCO Guideline. J Clin Oncol. 2024 Jul 20;42(21):2599-2615.

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy and Coverage Committee on 10/24/24.

GUIDELINE UPDATE INFORMATION:

11/15/03	Annual review. Developed separate policy for Genetic Testing for Inherited BRCA1 and BRCA2 Mutations. Added coverage and non-coverage statement for BRCA testing of men.
07/01/05	HCPCS update. Added S0265.
12/15/05	Biennial review. Coverage statement changed to reflect BCA policy. Non-coverage section reworded. Information added to Description section.
01/01/06	Annual HCPCS coding update: added 83900, 83907, 83908, 83909, and 83914; revised 83898 & 83901.
06/15/06	Revision to include new codes into limitation section.
10/15/06	Revision to coverage statement; definitions added.
01/01/07	Annual HCPCS coding update: added 96040, deleted 99401, 99402, 99403, 99404.
07/15/07	Annual review, coverage statements maintained, guideline reformatted, references updated.
01/01/08	Annual HCPCS coding update: revised 83898, 83900, 83901, and 83908.
01/01/09	Annual HCPCS coding update: descriptor revised for codes 83890, 83891, 83892, 83893, 83894, 83897, 83900, 83903, 83907, 83909, and 83914.
09/15/09	Annual review: position statements updated, description section, guideline title, and references updated.
10/15/09	Reimbursement Information section updated.
08/15/10	Annual review: position statements updated to include “cancer of fallopian tube or primary peritoneal cancer” to be considered along with breast and ovarian cancer in assessing family history; additional position statements added regarding CHEK2 testing and testing for minors; description section and references updated.
04/01/11	Revision; Certificate of Medical Necessity added.
08/15/11	Scheduled review; position statements and references updated; formatting changes.
01/01/12	Annual HCPCS update. Added CPT codes 81211-81217; revised Billing/Coding and Reimbursement Information sections.
04/01/12	Quarterly HCPCS update. Deleted codes S3818-S3823.
08/15/12	Annual review; position statements, description section, and references updated.
11/15/13	Annual review; position statements, program exception, and references updated.
11/15/14	Annual review; position statements and references updated.
07/15/15	Annual Review; position statements, program exception, and references updated.
01/01/16	Annual HCPCS/CPT update; code 81162 added.

08/15/16	Revision; position statement section and references updated.
02/15/17	Revision; position statements and references updated.
02/15/18	Revision; position statements and references updated.
01/01/19	Annual CPT/HCPCS coding update. Added codes 81163, 81167; revised codes 81162, 81212, 81215-81217; deleted codes 81211, 81213, 81214.
02/15/19	Revision; position statements updated and reorganized; policy title, description, and references updated.
02/15/21	Review; position statements and references updated.
03/15/23	Review: MCG title, position statements, coding, and references updated.
06/15/23	Revision; position statements updated.
11/15/24	Review: Position statements, description, and references updated.
01/01/25	Annual CPT/HCPCS coding update. Code 96041 added; code 96040 deleted.