BRCA 1 and BRCA 2 Genetic Testing

[For the list of services and procedures that need preauthorization, please refer to www.mcs.com.pr, go to "Comunicados a Proveedores" and click "Cartas Circulares".]

Medical Policy:	**MP-LB-01-19**
Original Effective Date:	**August 13, 2019**
Revised:	**September 27, 2023**
Next Revision:	**September, 2024**

Related Policies:

- **MP-LB-02-09 Genetic Testing for Adults and Children.**
- **MP-LB-01-09 Gene Expression Profiling Panel for use in the Management of Breast Cancer Treatment using (Oncotype DX™ Test).**

This policy applies to products subscribed by the following corporations, MCS Life Insurance Company (Commercial), and MCS Advantage, Inc. (Classicare) and Medical Card System, Inc., provider's contract; unless specific contract limitations, exclusions or exceptions apply. Please refer to the member's benefit certification language for benefit availability. Managed care guidelines related to referral authorization, and precertification of inpatient hospitalization, home health, home infusion and hospice services apply subject to the aforementioned exceptions.

DESCRIPTION

Germline genetic testing of BRCA1 and BRCA2 is available to identify individuals at increased risk for breast and ovarian cancers, as individuals with an inherited cancer syndrome may benefit from screening and prevention strategies to reduce their risk. The prevalence of BRCA mutations in the population is estimated between 1 in 300 and 1 in 800; however, specific mutations known as "founder mutations" occur more often in populations founded by a small ancestral group, including Ashkenazi (Eastern European) Jews, French Canadians, and Icelanders. The prevalence of BRCA mutations in the Ashkenazi Jewish population is approximately 1 in 40. Three recurrent BRCA1 and BRCA2 mutations have been identified in Ashkenazi Jewish individuals (i.e., a genetically distinct population of Jewish people of eastern and central European ancestry) and make up the vast majority of BRCA mutations that occur in this population.

Mutations in the BRCA1 and BRCA2 genes are passed down in families through an autosomal dominant inheritance pattern meaning that the associated cancer predisposition can be inherited through either the mother's or father's side of the family and transmitted by a male or female. When a parent carries a BRCA mutation, there is a 50% chance of passing down the gene mutation with every pregnancy. Although the risk of inheriting the predisposition from a parent who carries a mutation is 50%, not everyone with an inherited mutation will develop cancer. The likelihood that a woman with a mutation will develop a related cancer (i.e., penetrance of a BRCA mutation) is estimated between 41% and 90% and is much lower for men. The risk of developing cancer depends on numerous variables, including the penetrance of the specific mutation, the genetic makeup of the individual, environmental risk factors, the gender of the individual and their age.

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate member certificate and subscriber agreement contract for applicable diagnostic imaging, DME, laboratory, machine tests, benefits and coverage.

INDICATIONS

I. Medical Card System, Inc. (MCS) considers the use of **Genetic Assessment for Breast and/or Ovarian Cancer Syndrome** **medically necessary** for the Classicare (Advantage) LOB, under the criteria established within the Medicare LCD:

Local Coverage Determination for BRCA1 and BRCA2 Genetic Testing (L36499). Please refer to the aforementioned LCD for specific details regarding coverage indications, limitations and/or medical necessity.

II. Medical Card System, Inc. (MCS) considers the use of **Genetic Assessment for Breast and/or Ovarian Cancer Syndrome** **medically necessary** in patients who meet **one or more** of the following criteria (Applies to the Commercial LOB **Only**):

A. General Testing Criteria

1. Individuals with any blood relative with a known pathogenic or likely pathogenic variant in a cancer susceptibility gene.
2. Individuals meeting the criteria below but who tested negative with previous limited testing (eg, single gene and/or absent deletion duplication analysis) interested in pursuing multi-gene testing.
3. A pathogenic or likely pathogenic variant identified on tumor genomic testing that has clinical implications if also identified in the germline.
4. To aid in systemic therapy and surgical decision-making[b]
5. Individual who meets Li-Fraumeni syndrome (LFS) testing criteria or Cowden syndrome (CS)/*PTEN* hamartoma tumor syndrome (PHTS) testing criteria or Lynch syndrome (LS)
6. Testing *may* be considered in the following scenario (with appropriate pre-test education and access to post-test management):
    - An individual of Ashkenazi Jewish ancestry[c] without additional risk factors[d]
    - Personal history of serous endometrial cancer[e]

B. Testing Criteria for High-Penetrance Breast Cancer Susceptibility Genes

1. Personal history of breast cancer with specific features:
    - ≤50 years of age
    - Any age:
        - ◊ Treatment indications

- To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting[j,k]
- To aid in adjuvant treatment decisions with olaparib for high-risk,[l] HER2-negative breast cancer[j]

◊ Pathology/histology

- Triple-negative breast cancer
- Multiple primary breast cancers (synchronous or metachronous)[m]
- Lobular breast cancer with personal or family history of diffuse gastric cancer

◊ Male breast cancer

◊ Ancestry: Ashkenazi Jewish ancestry

◊ Family history[n]

- ≥ 1 close blood relative[o] with ANY:
  - breast cancer at age ≤50
  - male breast cancer
  - ovarian cancer
  - pancreatic cancer
  - prostate cancer with metastatic,[p] or high- or very-high-risk group (initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer)
- ≥ 3 diagnoses of breast cancer and/or prostate cancer (any grade) on the same side of the family including the patient with breast cancer

2. Family history of cancer

➢ Individuals affected with breast cancer (not meeting testing criteria listed above) or individual unaffected 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)[q].

➢ Individuals affected or unaffected with breast cancer who otherwise does not meet the criteria above but have a probability >5% of a BRCA1/2 pathogenic or likely pathogenic variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, CanRisk)[r]

3. Testing ***may*** be considered in the following scenarios (with appropriate pre-test education and access to post-test management):

    a. Personal history of breast cancer <60 y not meeting any of the above criteria may approach a 2.5% probability of having a probable or likely probable variant, based on recent data.[s] It is cautioned that the majority of those probable variants will be in moderate penetrance genes, which are over-represented in older affected individuals, and for which data on appropriate management are often lacking. Access to an experienced genetic counseling team to discuss management options is particularly important in this setting.

    b. Personal history of breast cancer diagnosed at any age with ≥1 close relative[o] with intermediate-risk prostate cancer with intraductal/cribriform histology. (see Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer)

    c. Individuals affected or unaffected with breast cancer who otherwise do not meet any of the above criteria but with a 2.5% – %5 probability of BRCA1/2 pathogenic or likely pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)[f]

Note[1]: Pathogenic variant (PV) – A genetic alteration that increases an individual's susceptibility or predisposition to a certain disease or disorder. When such a variant (or mutation) is inherited, development of symptoms is more likely, but not certain. Also called deleterious mutation, disease-causing mutation, predisposing mutation, and susceptibility gene mutation.

Note[2]: There is a low probability (<2.5%) that testing will have findings of documented high-penetrance genes in the following scenarios: a) Female diagnosed with breast cancer at age >60 years, with no close relative[o] with breast, ovarian, pancreatic, or prostate cancer, and b) Diagnosed with localized prostate cancer with Gleason Score <7 and no close relative[o] with breast, ovarian, pancreatic, or prostate cancer.

Note[a]: For further details regarding the nuances of genetic counseling and testing see Principles of Cancer Risk Assessment and Counseling at the National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline in Oncology for Genetic/Familial High-Risk Assessment Breast, Ovarian, and Pancreatic. Version 2.2024 – September 27, 2023.

Note[b]: E.g., PARP inhibitors for ovarian cancer, prostate cancer, pancreatic cancer, and metastatic HER2-negative breast cancer; platinum therapy for prostate cancer and pancreatic cancer; and risk-reducing surgery.

Note[c]: Testing for three founder pathogenic or likely pathogenic mutations for BRCA1/2 may be offered to individuals as early as age 18-25 years, who have one grandparent identified as of Ashkenazi Jewish ancestry, irrespective of cancer history in the family, as part of longitudinal studies. For those without access to longitudinal research studies, testing may be provided if there is access to pre-test education along with post-test counseling, additional genetic testing if indicated, and high-risk management. Testing should not be offered outside of a medical framework or clinical trial.

Note[d]: In addition to the BRCA1 and BRCA2 PV in those of Ashkenazi ancestry, there are other ancestries that demonstrate "Founder mutations." In these circumstances, the decision to test will depend on the prevalence of the PV in the local population, family history, clinical features, and age of cancer diagnosis. Some additional examples where ancestry may, along with personal and/or family history, contribute to decisions about genetic testing include the following associations: BRCA1 PV and Polish ancestry; BRCA2 PV and Icelandic ancestry; BRCA1 and BRCA2 PV in those of French Canadian ancestry; numerous BRCA1 and BRCA2 PV in those of Spanish, Mexican, and Central and South American descent; BRCA1 and BRCA2 PV and Bahamian ancestry; and BRCA1 and BRCA2 PV and Hungarian ancestry. The TP53 PV c.1010G>A (p.Arg337His) PV is seen in a subset of those of Brazilian ancestry, and CDKN2A founder c.225_243del (p.Ala76fs) in those of Dutch ancestry. While emerging data derived from populations of Asian, African, and Middle Eastern origin have documented recurring mutations in BRCA1 and BRCA2 and other genes, population allele frequency data are not yet available to inform testing individuals based solely on ancestry in the absence of personal and/or family history. The same is true for founder mutations in lower penetrance genes (e.g., CHEK2 c.1100delC in those of northern European ancestry), where family and personal history inform decisions for testing.

Note[e]: This is a rare subtype of uterine cancer for which there is evolving evidence of an association with BRCA 1P/LP variants.

Note[f]: Testing for pathogenic variants in other genes should take into consideration factors such as patient preferences, turnaround time, and insurance restrictions to particular labs (and thus particular panels). The prevalence of VUS increases with testing of additional genes. Individuals should have pre-test education on the challenges in managing pathogenic variants in genes associated with specific syndromes (e.g., *CDH1* and *TP53* given their expanding clinical phenotypes) in the absence of a family history typical of such syndromes (does not apply for de novo pathogenic variants). Patients should also have pre-test education regarding the uncertain clinical utility of identifying certain pathogenic variants (e.g., monoallelic *MUTYH*).

Note[g]: Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management.

Note[h]: For the purposes of this Medical Policy, invasive and ductal carcinoma in situ breast cancers should be included.

Note[i]: For personal or family history of ovarian cancer, see Section C; for pancreatic cancer, see CRIT-5 and for prostate cancer, see CRIT-6 in National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline in Oncology for Genetic/Familial High-Risk Assessment Breast, Ovarian, and Pancreatic Version 2.2024 – September 27, 2023.

Note[j]: Robson, M., et al. N Engl J Med 2017; 377:523-533. Litton, J.K., et al. N Engl J Med 2018; 379: 753-763

Note[k]: As indicated in the criteria, testing is recommended for all triple negative breast cancers, and these indications are specifically for PARP inhibitor eligibility

Note[l]: The definition of high-risk disease is that used in the Phase III OlympiA trial which compared adjuvant Olaparib to placebo among BRCA1/BRCA2 carriers with high-risk disease. (Tutt, A.N.J., et al. Engl J Med 2021; 384:2394-2405). The definition includes:

- Triple negative breast cancer treated with either:
  - adjuvant chemotherapy with axillary node-positive disease or an invasive primary tumor ≥2cm on pathology analysis, or
  - neoadjuvant chemotherapy with residual invasive breast cancer in the breast or resected lymph nodes.
- Hormone receptor positive disease treated with either:
  - adjuvant chemotherapy with ≥4 positive pathologically confirmed lymph nodes, or
  - neoadjuvant chemotherapy which did not have a complete pathologic response, with a CPS+EG score of 3 or higher.
- The CPS+EG scoring system is based on a combination of clinical and pathologic stage, estrogen receptor status and histologic grade. See Neoadjuvant Therapy Outcomes Calculator (Jeruss, J.S., et al. J Clin Oncol 2008; 26:246-252; Mittendorf, E.A., et al. J Clin Oncol 2011; 29:1956-1962). See NCCN Guidelines for Breast Cancer for further details.

Note[m]: Weitzel, J.N., et al. Breast Cancer Res Treat 2021; 188:759-768

Note[n]: Consideration of the limitations of unknown or limited family structure is indicated in those age ≥51.

Note[o]: Close blood relatives include first-, second-, and third-degree relatives on the same side of the family.

Note[p]: Metastatic prostate cancer is biopsy-proven and/or with radiographic evidence and includes distant metastasis and regional bed or nodes. It is not a biochemical recurrence only. Prostate cancer-specific mortality should be a surrogate for metastatic disease for family history purposes**.**

Note[q]: This may be extended to an affected third-degree relative if related through two male relatives (e.g., paternal grandfather's mother or sister). If the affected first-degree relative underwent genetic testing and is negative for detectable P/LP variants and there is no other family history of cancer, there is a low probability that any finding will have documented clinical utility.

Note[r]: The approximate 5% threshold for probability of carrying *BRCA1/2* pathogenic variants is utilized because of availability of prior probability models; however, it is recognized that current model estimates vary substantially, and that different thresholds may be appropriate if other genes are included in the model utilized. If genes other *BRCA1* and *BRCA2* are to be included in models evaluating the threshold for testing, the penetrance, clinical actionability, and phenotypic features of cancers associated with P/LP variants in these genes should be considered. The panel

encourages the development of validated models that include these parameters to determine eligibility and appropriateness for gene panel testing for inherited cancer risk. The models are only validated for *BRCA 1/2*.

Note[s]: Kurian A, et al. JAMA 2020;323:995-997.

Note[t]: For personal or family history of breast cancer, see Section B; for pancreatic cancer, see CRIT-5 and for prostate cancer, see CRIT-6 in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline in Oncology for Genetic/Familial High-Risk Assessment Breast, Ovarian, and Pancreatic. Version 2.2024 – September 27, 2023.

Note[u]: The listed genes differ in their levels of risk. See GENE-A in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline in Oncology for Genetic/Familial High-Risk Assessment Breast, Ovarian, and Pancreatic. Version 2.2024 – September 27, 2023 for specific risks.

Note[v]: *BRCA*-related ovarian cancers are associated with epithelial, non-mucinous histology. Lynch Syndrome (LS) can be associated with both non-mucinous and mucinous epithelial tumors. Be attentive for clinical evidence of LS (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal). Specific types of non-epithelial ovarian cancers and tumors can also be associated with other rare syndromes. Examples include an association between sex-cord tumors with annular tubules and PJS or Sertoli-Leydig tumors and DICER1-related disorders.

C. Testing Criteria for Ovarian Cancer Susceptibility Genes

1. See General Testing Criteria on Subsection A.

2. Personal history of epithelial ovarian cancer[v] (including fallopian tube cancer or peritoneal cancer) at any age

3. Family history of cancer only
   - An individual unaffected with ovarian cancer (with a first- or second-degree blood relative with epithelial ovarian cancer[v] (including fallopian tube cancer or peritoneal cancer) at any age[q]
   - An individual unaffected with ovarian cancer who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* P/LP variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)[r]

III. Medical Card System, Inc. (MCS) will determine the following specialists as qualified physicians to order **Genetic Assessment for Breast and/or Ovarian Cancer Syndrome** (Applies to the **Both** the Classicare and Commercial LOBs):

a. Geneticists and/or Hematologist-Oncologists

b. Gynecologists

c. Surgeons

d. Neurologists

LIMITATIONS (Applicable to Commercial LOB Only):

1. A specific test may only be performed once in a lifetime per beneficiary for inherited conditions. However, when medically reasonable and necessary, genetic testing may be done on acquired conditions such as malignancies (including separate malignancies developing at different times) as they are treated and are being followed, in order to assess response or other relevant clinical criteria. Likewise, there are situations where medical record and literature documentation are able to demonstrate that serial testing can be reasonably predicted to provide additional clinically useful information. When the record documents that this information, such as confirmed significant response to current therapy, is likely to assist in modifying treatment, serial testing can be considered reasonable and necessary and eligible for medical coverage.

2. Any procedures required prior to cell lysis (e.g., microdissection [CPT codes 88380 and 88381]) should be reported separately and utilization must be clearly supported based on the application and clinical utility. Such claims may be subject to prepayment medical review.

3. HCPCS code G0452 with modifier 26 should be used by pathologists when an interpretation of a molecular pathology test is performed. Nonphysician practitioners (e.g., PhD, scientists, etc.) are not eligible to report this code, only physicians may use/bill this code. This code should not be billed without modifier 26 since it is an interpretation code only.

4. Genetic testing for quality assurance purposes.

5. Providers are required to code to specificity. However, if CPT 81479 (unlisted molecular pathology procedure) is used the documentation must clearly identify the unique molecular pathology procedure performed. When multiple procedure codes are submitted on a claim (unique and/or unlisted) the documentation supporting each code should be easily identifiable.

DOCUMENTATION REQUIREMENTS:

a. Documentation must be adequate to verify that coverage guidelines listed above have been met. Thus, the medical record must contain documentation that the testing is expected to influence treatment of the condition toward which the testing is directed. The laboratory or billing provider must have on file the physician requisition which sets forth the diagnosis or condition (ICD-10-CM code) that warrants the test(s).

b. The submitted medical record must support the use of the selected ICD-10-CM code(s). The submitted CPT/HCPCS code must the service performed. When the documentation does not meet the criteria for the service rendered or the documentation does not

establish the medical necessity for the services, such services will be denied as **Not** reasonable and medically necessary.

RATIONALE

MCS framework is designed to improve access, outcomes, and our enrollee's experience of care and to ensure all enrollees achieve their best health. This policy acts as a guideline for nursing staff in the initial screening of service requests, meticulously upholding a hierarchy that prioritizes Local Coverage Determinations (LCDs) and National Coverage Determinations (NCDs) established by the Centers for Medicare & Medicaid Services (CMS), followed by our organization's medical policy, recognized medical association guidelines, and clinical decision-making processes. It is crafted to ensure that preliminary assessments are in harmony with these layers of guidance, underscoring that all final coverage determinations strictly adhere to the relevant LCDs and NCDs, while also considering the insights from recognized medical associations and the clinical judgment of healthcare professionals (MD's and DMD's) as necessary.

CODING INFORMATION

CPT® CODES (List may not be all inclusive)

CPT® Codes	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 (BRCA 1, 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 (BRCA 1, DNA repair associated), (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81166	BRCA1 (BRCA 1, 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; 18 5delAG, 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
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
81479	Unlisted Molecular Pathology Procedure
96040	Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family

Current Procedural Terminology (CPT®) 2023 American Medical Association: Chicago, IL.

Note$_2$: Do not report 81162 in conjunction with 81163, 81164, 81165, 81166, 81167, 81215, 81216, 81217, and 81432.

Note$_3$: To report BRCA1, BRCA2 full sequence analysis and full duplication/deletion analysis on the same date of service, use 81162.

HCPCS CODES (List may not be all inclusive)

HCPCS® Codes	DESCRIPTION
G0452	Molecular pathology procedure; physician interpretation and report
S0265	Genetic counseling, under physician supervision, each 15 minutes

2023 HCPCS LEVEL II Professional Edition® (American Medical Association).

ICD-10 CODES (Applies to Both Classicare and Commercial LOBs) (List may not be all inclusive)

ICD-10 Codes	DESCRIPTION
C25.0	Malignant neoplasm of head of pancreas
C25.1	Malignant neoplasm of body of pancreas
C25.2	Malignant neoplasm of tail of pancreas
C25.3	Malignant neoplasm of pancreatic duct
C25.4	Malignant neoplasm of endocrine pancreas
C25.7	Malignant neoplasm of other parts of pancreas
C25.8	Malignant neoplasm of overlapping sites of pancreas
C25.9	Malignant neoplasm of pancreas, unspecified
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C50.021	Malignant neoplasm of nipple and areola, right male breast

C50.022	Malignant neoplasm of nipple and areola, left male breast
C50.029	Malignant neoplasm of nipple and areola, unspecified male breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.119	Malignant neoplasm of central portion of unspecified female breast
C50.121	Malignant neoplasm of central portion of right male breast
C50.122	Malignant neoplasm of central portion of left male breast
C50.129	Malignant neoplasm of central portion of unspecified male breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.219	Malignant neoplasm of upper-inner quadrant of unspecified female breast
C50.221	Malignant neoplasm of upper-inner quadrant of right male breast
C50.222	Malignant neoplasm of upper-inner quadrant of left male breast
C50.229	Malignant neoplasm of upper-inner quadrant of unspecified male breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.319	Malignant neoplasm of lower-inner quadrant of unspecified female breast
C50.321	Malignant neoplasm of lower-inner quadrant of right male breast
C50.322	Malignant neoplasm of lower-inner quadrant of left male breast
C50.329	Malignant neoplasm of lower-inner quadrant of unspecified male breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.419	Malignant neoplasm of upper-outer quadrant of unspecified female breast
C50.421	Malignant neoplasm of upper-outer quadrant of right male breast
C50.422	Malignant neoplasm of upper-outer quadrant of left male breast
C50.429	Malignant neoplasm of upper-outer quadrant of unspecified male breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.519	Malignant neoplasm of lower-outer quadrant of unspecified female breast
C50.521	Malignant neoplasm of lower-outer quadrant of right male breast
C50.522	Malignant neoplasm of lower-outer quadrant of left male breast
C50.529	Malignant neoplasm of lower-outer quadrant of unspecified male breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast

C50.619	Malignant neoplasm of axillary tail of unspecified female breast
C50.621	Malignant neoplasm of axillary tail of right male breast
C50.622	Malignant neoplasm of axillary tail of left male breast
C50.629	Malignant neoplasm of axillary tail of unspecified male breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.819	Malignant neoplasm of overlapping sites of unspecified female breast
C50.821	Malignant neoplasm of overlapping sites of right male breast
C50.822	Malignant neoplasm of overlapping sites of left male breast
C50.829	Malignant neoplasm of overlapping sites of unspecified male breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.919	Malignant neoplasm of unspecified site of unspecified female breast
C50.921	Malignant neoplasm of unspecified site of right male breast
C50.922	Malignant neoplasm of unspecified site of left male breast
C50.929	Malignant neoplasm of unspecified site of unspecified male breast
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary
C56.9	Malignant neoplasm of unspecified ovary
C57.00	Malignant neoplasm of unspecified fallopian tube
C57.01	Malignant neoplasm of right fallopian tube
C57.02	Malignant neoplasm of left fallopian tube
C61	Malignant neoplasm of prostate
D05.00	Lobular carcinoma in situ of unspecified breast
D05.01	Lobular carcinoma in situ of right breast
D05.02	Lobular carcinoma in situ of left breast
D05.10	Intraductal carcinoma in situ of unspecified breast
D05.11	Intraductal carcinoma in situ of right breast
D05.12	Intraductal carcinoma in situ of left breast
D05.80	Other specified type of carcinoma in situ of unspecified breast
D05.81	Other specified type of carcinoma in situ of right breast
D05.82	Other specified type of carcinoma in situ of left breast
D05.90	Unspecified type of carcinoma in situ of unspecified breast
D05.91	Unspecified type of carcinoma in situ of right breast

D05.92	Unspecified type of carcinoma in situ of left breast
Z85.07	Personal history of malignant neoplasm of pancreas
Z85.3	Personal history of malignant neoplasm of breast
Z85.43	Personal history of malignant neoplasm of ovary
Z85.46	Personal history of malignant neoplasm of prostate

ICD-10 CODES For Family History (Applies to Commercial LOB Only) (List may not be all inclusive)

ICD-10 Codes	DESCRIPTION
Z15.01	Genetic susceptibility to malignant neoplasm of breast
Z15.02	Genetic susceptibility to malignant neoplasm of ovary
Z15.04	Genetic susceptibility to malignant neoplasm of endometrium
Z80.0	Family history of malignant neoplasm of digestive organs
Z80.3	Family history of malignant neoplasm of breast
Z80.41	Family history of malignant neoplasm of ovary
Z80.42	Family history of malignant neoplasm of prostate
Z80.49	Family history of malignant neoplasm of other genital organs
Z80.8	Family history of malignant neoplasm of other organs or systems

REFERENCES

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POLICY HISTORY

DATE	ACTION	COMMENT
August 13, 2019	**Origination of Policy**	**Approved by the MAC Committee with recommendations.**
August 26, 2019	**Revised**	**To the Indications Section:** • Added Section III. Which contains the following: Medical Card System, Inc. (MCS) will determine the following specialists as qualified physicians to order Genetic Assessment for Breast and/or Ovarian Cancer Syndrome (Applies to the Both the Classicare and Commercial LOBs): a. Geneticists and/or Hematologist-Oncologists, b. Gynecologists, c. Surgeons and d. Neurologists. The addition of adding specific specialties to the policy was recommended by the MAC Committee and the addition of the latter two specialties is in accordance with the Provider Network Management Department.
June 19, 2020	**Revised**	**References Updated. Deleted #9.** **To the Indications Information Section:** • To Section I: Updated Local Coverage Determination for BRCA1 and BRCA2 Genetic Testing (l36499) link address. • To Section II: Deleted: BRCA1/2 pathogenic/likely pathogenic variant* detected by tumor profiling on any tumor type in the absence of germline pathogenic/likely pathogenic variant analysis. Regardless of family history, some individuals with BRCA-related cancer may benefit from genetic testing to determine eligibility for targeted treatment. • To Section II: Deleted: 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. • To Section II Note a: Deleted: Testing of an individual without a cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing. Added: For further details regarding the nuances of genetic counseling and testing see Principles of Cancer Risk Assessment and Counseling.

		• To Section II Note b: Deleted: Irrespective of degree of relatedness. Added: Testing for pathogenic variants in other genes should take into consideration factors such as patient preferences, turnaround time, and insurance restrictions to particular labs (and thus particular panels). The prevalence of VUS increases with testing of additional genes. Individuals should have pre-test education on the challenges in managing pathogenic variants in genes associated with specific syndromes (eg, CDH1 and TP53 given their expanding clinical phenotypes) in the absence of a family history typical of such syndromes (does not apply for de novo pathogenic variants). Patients should also have pre-test education regarding the uncertain clinical utility of identifying certain pathogenic variants (eg, monoallelic MUTYH). • To Section II Note c: Deleted: For the purposes of this Medical Policy, invasive and ductal carcinoma in situ breast cancers should be included. Added: Meeting on or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management. • To Section II Note d: Added: For the purposes of this Medical Policy, invasive and ductal carcinoma in situ breast cancers should be included. • To Section II Note e: Deleted: First-degree relatives: parents, siblings, and children; second-degree relatives: grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings; third-degree relatives: great-grandparents, great-aunts, great-uncles, great-grandchildren, first cousins, and half aunts and uncles. • To Section II Note f: Deleted: Includes fallopian tube and primary peritoneal cancers. • To Section II Note g: Added: Approximately 2% - 5% of unselected cases of pancreatic adenocarcinoma will have a BRCA1/2 pathogenic/likely pathogenic variant. However, the disease is highly aggressive and the option to test the affective relative may not be available in the future. Thus, there may be significant benefit to family members in testing these patients near the time of diagnosis. In addition, increasing evidence suggests that identification of a BRCA 1/2 pathogenic likely pathogenic variant may direct use of targeted therapies for patients with pancreatic cancer. • To Section II Note h: Deleted: Testing for Ashkenazi Jewish founder-specific pathogenic/likely pathogenic variant(s) should be performed first. Comprehensive genetic testing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or if other BRCA-related criteria are met. Founder pathogenic/likely pathogenic variants exist in other populations. Added: Metastatic prostate cancer is biopsy-proven and/or with radiographic evidence and includes distant metastasis and regional bed or notes. It is not a biochemical recurrence only. Prostate cancer-specific mortality should be a surrogate of metastatic disease for family history purposes. • To Section II Note i: Deleted: Approximately 2%-5% of unselected cases of pancreatic adenocarcinoma will have a BRCA1/2 pathogenic/likely pathogenic variant. However, the disease is highly lethal and the option to test the affected relative may not be available in the future. Thus, there may be a significant benefit to family members in testing these patients near the time of diagnosis. In addition, increasing evidence suggests that identification of a BRCA1/2 pathogenic/likely pathogenic variant may direct use of targeted therapies for patients with pancreatic cancer. Added: Eg, PARP inhibitors for ovarian cancer, prostate cancer, pancreatic cancer, and

		metastatic HER2-negative breast cancer; platinum therapy for prostate cancer and pancreatic cancer. • To Section II Note j: Deleted: E.g., PARP inhibitors of ovarian cancer and metastatic HER2-negative breast cancer; platinum therapy for prostate cancer. Added: This may be extended to an affected third-degree relative if related through two male relatives (eg, paternal grandmother's mother or sister). If the affected first-degree relative underwent genetic testing and is negative for detectable mutations and there is no other family history of cancer, there is a low probability that any finding will have documented clinical utility. For probands with pancreatic cancer, only first-degree relatives should be offered testing unless indicated for other relatives based on additional family history. • To Section II Note k: Deleted: The may be extended to an affected third-degree relative if related through two male relatives (e.g., paternal grandfather's mother or sister). Added: The approximate 5% threshold for probability of carrying BRCA ½ pathogenic variants is utilized because of availability of prior probability models; however, it is recognized that current model estimates vary substantially, and that different thresholds may be appropriate if other genes are included in the model utilized. If genes other BRCA1 and BRCA2 are to be included in models evaluating the threshold for testing, the penetrance, clinical actionability, and phenotypic features of cancers associated with these mutations in these genes should be considered. The panel encourages the development of validated models that include these parameters to determine eligibility and appropriateness for gene panel testing for inherited cancer risk. The models are only validated for BRCA 1/2. • To Section II: added Note l: Testing for three founder mutations for BRCA1/2 maty be offered to unaffected men and women as early as age 18-25 years, who have one grandparent identified as of Ashkenazi Jewish ancestry, irrespective of cancer history in the family, as part of longitudinal studies, testing may be provided if there is access to pre-test education along with post-test counseling, additional genetic testing if indicated, and high risk management. Testing should not be offered outside of a medical framework or clinical trial. • To Section II: added Note m: Genes that are typically tested for pancreatic cancer risk include ATM, BRCA1, BRCa2, CDKN2A, most Lynch syndrome genes (MLH1, MSH2, MSH6, EPCAM), PALB2, STK11, and TP53. • To Section II: added Note n: Pancreatic cancer risk is higher in individuals of Ashkenazi Jewish descent. Genetic testing of Ashkenazi Jewish descent. Genetic testing of Ashkenazi Jewish patients with pancreatic cancer may have higher yield of mutations than of non-Ashkenazi Jewish patients. • To Section II: added Note o: Testing of first-degree relatives should only be done if it is impossible to test the individual who has pancreatic cancer. Some second-degree relatives may meet testing criteria based on additional family history. • To Section II – First bullet: Modified to read as follows: Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene. • To Section II – Second bullet: Modified to read as follows: Individuals meeting the criteria below but with previous limited testing (eg, single gene and/or absent deletion duplication analysis) interested in pursuing multi-gene testing. • To Section II – Third Bullet: Modified to read: • Personal history of cancer

		• Breast cancer plus one more of the following:
		  • Diagnosed ≤45 years of age
		  • Diagnosed 46-50 years of age with:
		  • An unknown or limited family history; or
		  • A second breast cancer primary at any age; or
		  • ≥1 close blood relative with breast, ovarian, pancreatic, or high-grade (Gleason score ≥7) or intraductal prostate cancer at any age; or
		• Diagnosed ≤60 years of age with triple-negative breast cancer;
		• Diagnosed at any age with:
		  • Ashkenazi Jewish ancestry; or
		  • ≥1 close blood relative with breast cancer diagnosed ≤50 years of age or ovarian, pancreatic, or metastatic or intraductal prostate cancer at any age; or
		  • ≥2 total diagnoses of breast cancer in patient and/or close blood relatives
		• Diagnosed at any age with male breast cancer
		• Added new indication: Epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age
		• Added new indication: Exocrine pancreatic cancer at any age
		• Added new indication: High grade (Gleason score ≥7) prostate cancer with:
		• Ashkenazi Jewish Ancestry; or
		• ≥1 close relative with breast cancer at age ≤50 years or ovarian, pancreatic, or metastatic or intraductal prostate cancer at any age; or
		• ≥2 close relatives with breast cancer or prostate cancer (any grade) at any age.
		• Added new indication: A mutation identified on tumor genomic testing that has clinical implications if also identified in the germline
		• To aid in systemic therapy decision-making such as HER2-negative metastatic breast cancer
		• Added new indication #4: Family history of cancer
		  • An affected or unaffected individual with a first- or second- degree blood relative meeting any of the criteria listed above (except individuals who meet criteria only for systemic therapy-decision-making)
		• Added new indication under #4, first bullet: And affected and unaffected individual who otherwise does not meet the criteria above has a probability >5% of a BRCA1/2 pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, Pennll)
		• Added new indication under #4, second bullet: Testing may be considered in the following scenarios (with appropriate pre-test education and access to post-test management);
		1. Bilateral breast cancer, first diagnosed between ages 50-65 yrs.
		2. An unaffected Ashkenazi Jewish individual
		3. An affected or unaffected individual who otherwise does not meet any of the above criteria but with a 2.5%-%5 probability of BRCA1/2 pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, Pennll)
		• Modified single note with asterisk as new Note 1.
		• Added new Note 2, which reads: There is a low probability (<2.5%) that testing will have findings of documented clinical utility in the following scenarios: a) Women diagnosed with breast cancer at age >65 years, with no close relatives with breast, ovarian, pancreatic, or prostate cancer, and b) Men diagnosed with localized prostate cancer with Gleason Score <7

		and no close relatives with breast, ovarian, pancreatic, or prostate cancer. **To the Limitations Section:** • To #1 – Deleted: Repeat genetic testing is Not covered. In general, diagnostic genetic testing for a disease should be performed once in a lifetime for an inherited condition. Added portions to sentence to first sentence "A specific test may only be performed". • To #1- 2nd sentence: Modified term "whenever" to "when". **To the Documentations Requirements Section:** • Deleted b: Documentation requirements of the performing laboratory (when requested) include, but are not limited to, lab accreditation, test requisition, test record/procedures, reports (preliminary and final), and quality control record. • Deleted c: Documentation requirements for LDT(s) (Lab Developed Tests) / protocols (when requested) include diagnostic test/assay, lab/manufacturer, names of comparable assays/services (if relevant), description of assay, analytical validity evidence, clinical validity evidence, and clinical utility. • To e: Added: The submitted medical record must support the use of the selected ICD-10-CM code(s). The submitted CPT/HCPCS code must the service performed. **To the Coding Information Section:** • Added CPT Code 81433 and 81479. • Added ICD-10 Code Z85.3.
June 17, 2021	**Revised**	**To the Indications Section:** • **To the Section II:** ➢ Phrase "Tested Negative" was added to the criteria II2. ➢ Specific Cancer were deleted according to NCCN 2021 from II3. ➢ Phrase "/ cribiform histology, or high or very high-risk group" was added to II3. ➢ Phrases "Any risk group" and "the following family history" were added to II3. ➢ Word Bilateral was deleted and Phrase "Multiple Primary" was added to the II.4.1 ➢ Word "Unaffected" was deleted from II.4.2 ➢ New information was added to the Note "a". ➢ Word "Mother" was deleted and Substitute by the word "Father" according NCCN page CRIT-2A in NOTE "j". ➢ Information was deleted according to NCCN page CRIT-2A from Note J. Under Testing Criteria for High Penetrance Breast and/or Ovarian Cancer Susceptibility Genes. ➢ Word "Unaffected" was deleted from Note L according to NCCN page CRIT-2A. ➢ Sentence "Genetic testing of Ashkenazi Jewish descent" was deleted from the Note "N" according to NCCN page CRIT-3. **To the Coding Section:** • **To the CPT Code Box:** ➢ CPT Codes 81445 and 81455 were deleted and removed according to the Instruction included in the LCA A57449. ➢ CPT Code 81215 was added to the note 2.

		• **<u>To the ICD-10 Code Box</u>:** **<u>The following ICD-Code were deleted from this Policy</u>**: C50.919, Z80.51, and Z80.6. **<u>To the References Section</u>:** • **<u>The following References were added to the Policy</u>:** #9 and 12. • **<u>The following References were deleted from this Policy</u>:** #4 and 6.
September 27, 2023	**Revised**	**References updated. Deleted former #1 & #7. Added new #1, 3, 6 &12.** **<u>To the Indications Section:</u>** • **To the Indications Section II:** • **Added new Subsection "A. General Testing Criteria".** – To #3: Deleted subtitle "Breast cancer plus one more of the following". – To new #3: Added: A pathogenic or likely pathogenic variant identified on tumor genomic testing that has clinical implications if also identified in the germline. – Added new #4: To aid in systemic therapy and surgical decision-making[b] – Added new #5: Individual who meets Li-Fraumeni syndrome (LFS) testing criteria or Cowden syndrome (CS)/PTEN hamartoma tumor syndrome (PHTS) testing criteria or Lynch syndrome (LS) – Added new #6: Testing may be considered in the following scenario (with appropriate pre-test education and access to post-test management): • An individual of Ashkenazi Jewish ancestry[c] without additional risk factors[d] • Personal history of serous endometrial cancer[e] – Added new subsection "B. Testing Criteria for High-Penetrance Breast Cancer Susceptibility Genes" – To Subsection B, bullet #1: modified age to ≤50 y – To second bullet, added: ♢ Treatment indications – To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting[j,k] – To aid in adjuvant treatment decisions with olaparib for high-risk,[l] HER2-negative breast cancer[j] – To second sub-bullet, also added: ♢ Pathology/histology – Triple-negative breast cancer – Multiple primary breast cancers (synchronous or metachronous)[m] – Lobular breast cancer with personal or family history of diffuse gastric cancer – To Second bullet, 2nd sub-bullet: Deleted A second breast cancer primary at any age. Added: - Individuals affected with breast cancer (not meeting testing criteria listed above) – To Second bullet, 3rd sub-bullet: Modified superscript to letter g and added term prostate. – Added new 5th sub-bullet, which reads: ♢ Family History[n] ○ ≥1 close blood relative with ANY: – breast cancer at age ≤ 50 – male breast cancer – ovarian cancer – pancreatic cancer with metastatic,[p] or high- or very-high risk group (Initial Risk Stratification

		and Staging Workup in NCCN Guidelines for Prostate Cancer) – ≥3 total diagnoses of breast prostate cancer any (any grade) or the same side of the family including the patient with breast cancer • To bullet #2: Deleted the following bullets: ➢ Diagnosed ≤60 years of age with triple-negative breast cancer; ➢ Diagnosed at any age with: o Ashkenazi Jewish ancestry; or o ≥1 close blood relative[e] with breast cancer diagnosed ≤50 years of age or ovarian, pancreatic, or metastatic or intraductal/ cribiform histology, or high or very high-risk group prostate cancer at any age; or o ≥3 total diagnoses of breast cancer in patient and/or close blood relatives[e] ➢ Diagnosed at any age with male breast cancer Epithelial ovarian cancer[f] (including fallopian tube cancer or peritoneal cancer) at any age ➢ Exocrine pancreatic cancer at any age[g] ➢ Metastatic or intraductal/ cribiform histology, or high or very high-risk group prostate cancer at any age ➢ Any risk group High prostate cancer with the following family history: ➢ ≥1 close relative[e] with breast cancer at age ≤50 years or ovarian, pancreatic, or metastatic or intraductal/ cribriform prostate cancer at any age; or ➢ ≥2 close relatives[e] with breast cancer or prostate cancer (any grade) at any age. ▪ A mutation identified on tumor genomic testing that has clinical implications if also identified in the germline ▪ To aid in systemic therapy decision-making such as HER2-negative metastatic breast cancer[i] – To Bullet #2, sub-bullet #1 under Family history of cancer: Added phrase "Individuals affected with breast cancer (not meeting testing criteria listed above). – To #2, 2nd bullet: Replaced probability model "Pennll" with "CanRisk" and replaced former superscript with letter r. – To #2, deleted bullet #2: Multiple primary Bilateral breast cancers, first diagnosed between ages 50 - 65 yrs. – To new #3: Added: Testing may be considered in the following scenarios (with appropriate pre-test education and access to post-test management): a. Personal history of breast cancer <60 y not meeting any of the above criteria may approach a 2.5% probability of having a probable or likely probable variant, based on recent data.[s] It is cautioned that the majority of those probable variants will be in moderate penetrance genes, which are over-represented in older affected individuals, and for which data on appropriate management are often lacking. Access to an experienced genetic counseling team to discuss management options is particularly important in this setting. – Personal history of breast cancer diagnosed at any age with ≥1 close relative[e] with intermediate-risk prostate cancer with intraductal/cribriform histology.

		(see Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer) – To bullet 3-c: Added 2.5% and replaced probability model "Pennll" with "CanRisk" and replaced former superscript with letter f. – To Note 2: Replaced "clinical utility" with "high-penetrance genes". To scenario a: Also replaced term women with "female", modified age >65 to >60 and modified superscript following relative with letter o. – To Note a: Modified year to Version 2.2024 – September 27, 2023. – Modified Note b to read: "E.g., PARP inhibitors for ovarian cancer, prostate cancer, pancreatic cancer, and metastatic HER2-negative breast cancer; platinum therapy for prostate cancer and pancreatic cancer; and risk-reducing surgery." – To note c: Modified to read as follows: Testing for three founder pathogenic or likely pathogenic mutations for BRCA1/2 may be offered to individuals as early as age 18-25 years, who have one grandparent identified as of Ashkenazi Jewish ancestry, irrespective of cancer history in the family, as part of longitudinal studies. For those without access to longitudinal research studies, testing may be provided if there is access to pre-test education along with post-test counseling, additional genetic testing if indicated, and high-risk management. Testing should not be offered outside of a medical framework or clinical trial. – No new note D, Added: In addition to the BRCA1 and BRCA2 PV in those of Ashkenazi ancestry, there are other ancestries that demonstrate "Founder mutations." In these circumstances, the decision to test will depend on the prevalence of the PV in the local population, family history, clinical features, and age of cancer diagnosis. Some additional examples where ancestry may, along with personal and/or family history, contribute to decisions about genetic testing include the following associations: BRCA1 PV and Polish ancestry; BRCA2 PV and Icelandic ancestry; BRCA1 and BRCA2 PV in those of French Canadian ancestry; numerous BRCA1 and BRCA2 PV in those of Spanish, Mexican, and Central and South American descent; BRCA1 and BRCA2 PV and Bahamian ancestry; and BRCA1 and BRCA2 PV and Hungarian ancestry. The TP53 PV c.1010G>A (p.Arg337His) PV is seen in a subset of those of Brazilian ancestry, and CDKN2A founder c.225_243del (p.Ala76fs) in those of Dutch ancestry. While emerging data derived from populations of Asian, African, and Middle Eastern origin have documented recurring mutations in BRCA1 and BRCA2 and other genes, population allele frequency data are not yet available to inform testing individuals based solely on ancestry in the absence of personal and/or family history. The same is true for founder mutations in lower penetrance genes (e.g., CHEK2 c.1100delC in those of northern European ancestry), where family and personal history inform decisions for testing. – To new note e no reads: This is a rare subtype of uterine cancer for which there is evolving evidence of an association with BRCA 1P/LP variants.

		– Deleted former note f, and replaced with: Testing for pathogenic variants in other genes should take into consideration factors such as patient preferences, turnaround time, and insurance restrictions to particular labs (and thus particular panels). The prevalence of VUS increases with testing of additional genes. Individuals should have pre-test education on the challenges in managing pathogenic variants in genes associated with specific syndromes (e.g., CDH1 and TP53 given their expanding clinical phenotypes) in the absence of a family history typical of such syndromes (does not apply for de novo pathogenic variants). Patients should also have pre-test education regarding the uncertain clinical utility of identifying certain pathogenic variants (e.g., monoallelic MUTYH). – Former Note g was replaced with: Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management. – A new note h reads: For the purposes of this Medical Policy, invasive and ductal carcinoma in situ breast cancers should be included. – New note i now reads: For personal or family history of ovarian cancer, see Section C; for pancreatic cancer, see CRIT-5 and for prostate cancer, see CRIT-6 in National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline in Oncology for Genetic/Familial High-Risk Assessment Breast, Ovarian, and Pancreatic Version 2.2024 – September 27, 2023. – A new note j was added: Robson, M., et al. N Engl J Med 2017; 377:523-533. Litton, J.K., et al. N Engl J Med 2018; 379: 753-763 – Added new note[k,] which reads: As indicated in the criteria, testing is recommended for all triple negative breast cancers, and these indications are specifically for PARP inhibitor eligibility – Added new note[l]: The definition of high-risk disease is that used in the Phase III OlympiA trial which compared adjuvant Olaparib to placebo among BRCA1/BRCA2 carriers with high-risk disease. (Tutt, A.N.J., et al. Engl J Med 2021; 384:2394-2405). The definition includes: • Triple negative breast cancer treated with either: – adjuvant chemotherapy with axillary node-positive disease or an invasive primary tumor ≥2cm on pathology analysis, or – neoadjuvant chemotherapy with residual invasive breast cancer in the breast or resected lymph nodes. • Hormone receptor positive disease treated with either: – adjuvant chemotherapy with ≥4 positive pathologically confirmed lymph nodes, or – neoadjuvant chemotherapy which did not have a complete pathologic response, with a CPS+EG score of 3 or higher. • The CPS+EG scoring system is based on a combination of clinical and pathologic stage, estrogen receptor status and histologic grade.

		See Neoadjuvant Therapy Outcomes Calculator (Jeruss, J.S., et al. J Clin Oncol 2008; 26:246-252; Mittendorf, E.A., et al. J Clin Oncol 2011; 29:1956-1962). See NCCN Guidelines for Breast Cancer for further details. – Added new note m: Weitzel, J.N., et al. Breast Cancer Res Treat 2021; 188:759-768 – Added new note n: Consideration of the limitations of unknown or limited family structure is indicated in those age ≥51. – Added new note o: Close blood relatives include first-, second-, and third-degree relatives on the same side of the family. – Added new note p: Metastatic prostate cancer is biopsy-proven and/or with radiographic evidence and includes distant metastasis and regional bed or nodes. It is not a biochemical recurrence only. Prostate cancer-specific mortality should be a surrogate for metastatic disease for family history purposes. – Added new note q: This may be extended to an affected third-degree relative if related through two male relatives (e.g., paternal grandfather's mother or sister). If the affected first-degree relative underwent genetic testing and is negative for detectable P/LP variants and there is no other family history of cancer, there is a low probability that any finding will have documented clinical utility. – Added new note r: The approximate 5% threshold for probability of carrying BRCA1/2 pathogenic variants is utilized because of availability of prior probability models; however, it is recognized that current model estimates vary substantially, and that different thresholds may be appropriate if other genes are included in the model utilized. If genes other BRCA1 and BRCA2 are to be included in models evaluating the threshold for testing, the penetrance, clinical actionability, and phenotypic features of cancers associated with P/LP variants in these genes should be considered. The panel encourages the development of validated models that include these parameters to determine eligibility and appropriateness for gene panel testing for inherited cancer risk. The models are only validated for BRCA 1/2. – Added new note s: Kurian A, et al. JAMA 2020;323:995-997. – Added new note t: For personal or family history of breast cancer, see Section B; for pancreatic cancer, see CRIT-5 and for prostate cancer, see CRIT-6 in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline in Oncology for Genetic/Familial High-Risk Assessment Breast, Ovarian, and Pancreatic. Version 2.2024 – September 27, 2023. – Added new note u: The listed genes differ in their levels of risk. See GENE-A in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline in Oncology for Genetic/Familial High-Risk Assessment Breast, Ovarian, and Pancreatic. Version 2.2024 – September 27, 2023 for specific risks. – Added new note v: BRCA-related ovarian cancers are

		associated with epithelial, non-mucinous histology. Lynch Syndrome (LS) can be associated with both non-mucinous and mucinous epithelial tumors. Be attentive for clinical evidence of LS (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal). Specific types of non-epithelial ovarian cancers and tumors can also be associated with other rare syndromes. Examples include an association between sex-cord tumors with annular tubules and PJS or Sertoli-Leydig tumors and DICER1-related disorders. – Added new Section C: Testing Criteria for Ovarian Cancer Susceptibility Genes – Added new C-1, which reads: See General Testing Criteria on Subsection A. – Added new C-2, which reads: Personal history of epithelial ovarian cancer[v] (including fallopian tube cancer or peritoneal cancer) at any age – Added new C-3, which reads: Family history of cancer only – An individual unaffected with ovarian cancer (with a first- or second-degree blood relative with epithelial ovarian cancerv (including fallopian tube cancer or peritoneal cancer) at any age[q] – An individual unaffected with ovarian cancer who otherwise does not meet the criteria above but has a probability >5% of a BRCA1/2 P/LP variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)[r] **To the Limitations Section:** • To #5: Deleted sentence: If on review the contractor cannot link a billed code to the documentation, these services will be denied. All changes were approved at the MAC meeting.
April 11, 2024	**UMC Approval**	