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Genetic Testing for Breast, Ovarian, Pancreatic, and Prostate Cancers

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I. Policy Description

BRCA1 and BRCA2 are two distinct tumor suppressor genes involved in a common DNA repair process (Roy et al., 2012). Germline mutations of BRCA genes are associated with an increased risk of breast and ovarian cancer, as well as other cancer types, including pancreatic and prostate cancer to a lesser extent (Paul & Paul, 2014).

"Prior to 2020, the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian (Breast, Ovarian, and Pancreatic as of 2020) focused largely on testing criteria for BRCA1/2 and appropriate risk management for carriers of a BRCA1 or BRCA2 P/LP variant. Sections on LFS and Cowden syndrome/PTEN hamartoma tumor syndrome (PHTS) were also included. Based on strong evidence that genes beyond BRCA1/2, TP53, and PTEN confer markedly increased risk of breast and/or ovarian cancers, these Guidelines have been expanded" (NCCN, 2023b) to include BRCA1, BRCA2, CDH1, PALB2, PTEN, and TP53 as high-penetrance breast cancer susceptibility genes, as well as some moderate-penetrance susceptibility genes. These susceptibility genes are often found on multi-gene panels, in addition to BRCA1/2.

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

The following coverage criteria are designed from National Comprehensive Cancer Network (NCCN) guidelines. "NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. In this [policy], the terms males and females refer to sex assigned at birth."
Consideration of both maternal and paternal family histories is necessary in the evaluation of individuals for risk of carrying a mutation in the BRCA1 or BRCA2 gene; each lineage must be considered separately.

1) For individuals without a diagnosis of a BRCA-related cancer who are at least 18 years of age, who have received genetic counseling, and who are in a family with a pathogenic familial gene mutation associated with breast cancer, the following testing **MEETS COVERAGE CRITERIA**:

a) Testing restricted to the known familial mutation.
b) Comprehensive genetic testing, including muti-gene panel testing, when the specific familial mutation is unknown.

2) For individuals who have received genetic counseling, multi-gene panel testing for gene mutations associated with breast, ovarian, pancreatic, or prostate cancer **MEETS COVERAGE CRITERIA** when **one** of the following conditions are met:
   a) The individual has been diagnosed with breast cancer **and** meets at least one of the following conditions:
      i) Was diagnosed before 51 years of age.
      i) Was diagnosed at any age with at least one of the following conditions:
         (a) High-risk, HER2-negative breast cancer
         (b) Lobular breast cancer with a personal or family history of diffuse gastric cancer.
         (c) Metastatic breast cancer.
         (d) Triple negative breast cancer.
         (e) Two or more primary breast cancer diagnoses.
         (f) Male breast cancer.
         (g) Has at least one close blood relative (see Note 1) with **any** of the following:
            (i) Breast cancer before 51 years of age.
            (ii) Breast cancer at any age in a male.
            (iii) Ovarian cancer at any age.
            (iv) Pancreatic cancer at any age.
            (v) Prostate cancer that is metastatic or a high- or very-high risk group prostate cancer (see Note 2) at any age.
         (h) Has a combined total of at least three diagnosed cancers (breast or prostate) in a single lineage of close blood relatives (see Note 1) (including the individual).
      ii) Is of Ashkenazi Jewish ancestry.
   b) The individual has been diagnosed with ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age.
   c) The individual has been diagnosed with pancreatic cancer at any age.
   d) The individual has been diagnosed with prostate cancer at any age with at least **one** of the following conditions:
      i) Has metastatic cancer, the tumor has intraductal/cribriform histology, or a high- or very-high risk group (see Note 2).
      ii) Has **any** of the following family history:
         (a) Ashkenazi Jewish ancestry.
         (b) At least one close blood relative (See Note 1) with **any** of the following:
            (i) Breast cancer before 51 years of age.
            (ii) Breast cancer at any age in a male.
            (iii) Ovarian cancer at any age.
            (iv) Pancreatic cancer at any age.
            (v) Prostate cancer that is metastatic or a high- or very-high risk group prostate cancer (see Note 2) at any age.

e) The individual has a gene mutation associated with breast, ovarian, pancreatic, or prostate cancer that was detected by tumor genomic profiling in the absence of germline mutation testing.
f) The individual meets testing criteria for Li-Fraumeni syndrome (LFS), Lynch syndrome, or Cowden syndrome/PTEN hamartoma tumor syndrome.

3) For individuals with a known family history of BRCA-related cancer who have received genetic counseling and are at least 18 years of age, multi-gene panel testing for gene mutations associated with breast, ovarian, pancreatic, or prostate cancer **MEETS COVERAGE CRITERIA** only if the family mutation is unknown (i.e., family member is unavailable for testing or testing results are unavailable) **and** at least one of the following conditions are met:
   a) The individual has at least one close blood relative (see Note 1) meeting any of the above criteria for an individual with cancer, **except as noted below**:
      i) Only first-degree relatives of an individual affected with pancreatic or prostate cancer should be offered testing.
   b) The individual has a family member with breast, ovarian, tubal, or peritoneal cancer with positive screening results (probability of 5% or greater) from a tool (see Note 3) designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (BRCA1 or BRCA2).
4) For individuals of Ashkenazi Jewish ancestry with no personal or family history of BRCA related cancers, testing for the three known founder mutations (185delAG and 518insC in BRCA1; 617delT in BRCA2) **MEETS COVERAGE CRITERIA**.
5) Testing for gene mutations associated with breast, ovarian, pancreatic, or prostate cancer D**OES NOT MEET COVERAGE CRITERIA** for **any** of the following:
   a) General population screening.
   b) Women diagnosed with breast cancer who are over 65 years of age and who have no close blood relative (see Note 1) with breast, ovarian, pancreatic, or prostate cancer, as there is a low probability that testing will have findings of documented clinical utility.
   c) Individuals diagnosed with localized prostate cancer with Gleason Score <7 and who have no close blood relative (see Note 1) with breast, ovarian, pancreatic, or prostate cancer, as there is a low probability that testing will have findings of documented clinical utility.
   d) In all other situations not specified above.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

6) Testing family members for a variant of uncertain significance **DOES NOT MEET COVERAGE CRITERIA.**

NOTES:

Note 1: Close blood relatives include 1st-degree relatives (e.g., parents, siblings, and children), 2nd-degree relatives (e.g., grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings), and 3rd-degree relatives (great-grandparents, great-aunts, great-uncles, great-grandchildren, and first

cousins), all of whom are on the same side of the family.

Note 2: Risk groups are defined in NCCN Guidelines for Prostate Cancer.
Note 3: According to the USPSTF recommendation in 2019, the risk tools evaluated by the USPSTF include the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, 7-Question Family History Screening Tool, International Breast Cancer Intervention Study instrument (Tyrer-Cuzick), and brief versions of BRCAPRO. They do not specifically state the preference of one tool over any of the others listed. According to the USPSTF, "these tools should be used to guide referrals to genetic counseling" (USPSTF, 2019).

III. Table of Terminology

Term	Definition
AA	African American
ACOG	The American College of Obstetricians and Gynecologists
AJ	Ashkenazi Jewish
ASBS	The American Society of Breast Surgeons
ASCO	American Society of Clinical Oncology
ATM	Ataxia telangiectasia mutated
BRCA	*Breast cancer gene*
BRCA1	*Breast cancer gene 1*
BRCA2	*Breast cancer gene 2*
CDH1	*cadherin 1*
CDRH	Center for Devices and Radiological Health
CHEK2	*Checkpoint kinase 2*
CLIA '88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid Services
CRPC	Castrate-resistant prostate cancer
dMMR	Mismatch despair deficiency
DNA	Deoxyribonucleic acid
EDTA	Ethylenediamine tetraacetic acid
ER	Estrogen receptor
FANCC	FA complementation group c
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FGFR2	Fibroblast growth factor receptor 2
GIS	Genomic instability score
HBOC	Hereditary Breast and Ovarian Cancer
HER-2	*Human epidermal growth factor 2*
LDTs	Laboratory-developed tests
LFS	Li-Fraumeni syndrome
MSH2	*Muts homolog 2*

MSI	Microsatellite instability
NBN	*Nibrin*
NCCN	National Comprehensive Cancer Network
NGS	Next-generation sequencing
NICE	National Institute for Health and Care Excellence
OCCR	Ovarian cancer cluster region
PALB2	*Partner and localizer of brca2*
PARP	*Poly ADP-ribose polymerase*
PCR	Polymerase chain reaction
PMS2	Pms1 homolog 2, mismatch repair system component
PR	Progesterone receptor
PTEN	*Phosphatase and tensin homolog*
RAD51C	*Rad51 paralog c*
RAD51D	*RAD51 homolog C*
RECQL	*RecQ Like Helicase*
RET	*Ret proto-oncogene*
SMARCA4	*Swi/snf related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4*
TMB	Tumor mutational burden
TP53	*Tumor protein p53*
USPSTF	The U.S. Preventive Services Task Force

IV. Scientific Background

BRCA1 and *BRCA2* are critical genes in the process of homologous recombination repair of double-strand DNA breaks (Walsh, 2015). Both genes are very large (occupying about 70 kb) and encode a combined total of 49 exons. They are considered tumor suppressor genes and a loss of function on either gene increases the cancer risk (Pan & Xie, 2017). *BRCA1* is thought to regulate c-Abl kinase activity (as loss of *BRCA1* results in a constitutively activated c-Abl kinase) whereas *BRCA2* is thought to regulate Rad51, which repairs DNA damage such as chromosomal breaks (Yoshida & Miki, 2004).

Different regions of mutation may confer different types of risk. For example, *BRCA2* has an area called the ovarian cancer cluster region (OCCR) in which mutations predispose the patient for ovarian cancer. Mutations outside the OCCR are more likely to result in breast cancer compared to mutations in the OCCR. On *BRCA1*, mutations closer to the 3' end of the gene may result in higher risk than mutations closer to the 5' end (Meric-Bernstam et al., 2013). Other gene defects that affect homologous recombination include hypermethylation of *RAD51C* or *ATR* mutation. However, these are considered to have a phenotype of "BRCAness" and behave like *BRCA*-deficient genes even if the *BRCA* gene itself is normal (Walsh, 2015).

Although the probability of cancer development in carriers is variable, estimates of penetrance in individuals with a pathogenic variant in *BRCA1* or *BRCA2* range from 46% to 87% lifetime risk for breast cancer, and 16.5% to 63% lifetime risk for ovarian cancer (Petrucelli et al., 2016).

BRCA1 and *BRCA2* mutations account for about 5 – 10% of breast cancers and 10 – 18% of ovarian cancers (Walsh, 2015). *BRCA* mutations are inherited in an autosomal dominant fashion and are highly penetrant (Isaacs & Peshkin, 2023).

It is clinically important to recognize these carriers to guide management of cancer and identify unaffected women with a *BRCA* mutation who will benefit from enhanced surveillance; in addition, recognizing carriers helps physicians tailor care to improve outcomes and more efficiently use health-care resources. Adherence to guidelines for managing cancer risk has the potential to have a significant individual and population health impact on morbidity and mortality (Buchanan et al., 2017). For example, *BRCA* deficient cancers are often targeted for a certain class of drugs called poly(ADP-ribose) polymerase (PARP) inhibitors. These inhibitors target enzymes responsible for the base excision repair pathway. A cell can survive with the loss of either the base excision repair pathway or the homologous recombination mechanism, but not both. Since *BRCA*-deficient cells already have a faulty homologous recombination mechanism, the *BRCA*-deficient cell dies when the PARP inhibitor shuts down the base excision repair pathway. *BRCA*-deficient cells have been shown to be affected 1000 times more by these PARP inhibitors than wild-type cells (Walsh, 2015).

Numerous proprietary tests exist for the assessment of *BRCA* or its related genes such as *RAD51*. For example, gene panels such as Ambry Genetics' panel include 25 genes such as *BRCA1*, *BRCA2*, *CHEK2*, *ATM*, *RAD51C*, and *BRIP1*. This test is performed by next generation sequencing or Sanger sequencing (except for *EPCAM*) with a turnaround time of 2-3 weeks. Ambry has several proprietary tests such BRCAplus and BreastNext (Ambry, 2023). Another gene panel that has been developed to identify genetic mutations associated with inherited breast and ovarian cancers is the AmpliSeq for Illumina *BRCA* Plus, Extended Hereditary Breast and Ovarian Research Panel. This panel assesses germline variants in 11 genes known to harbor mutations related to breast and ovarian cancer: *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C*, *RAD51D*, *NBN*, *CDH1*, *SMARCA4*, and *TP53*. However, though these community panels boasts the convenience of being made-to-order, Illumina warns that they do not have associated performance metrics (Illumina, 2021). myChoice CDx by Myriad Genetics, Inc. is a tumor test that determines homologous recombination deficiency status by detecting *BRCA1* and *BRCA2* (sequencing and large rearrangement) variants. This next generation sequencing-based *in vitro* diagnostic assay focuses on assessing genomic instability by using loss of heterozygosity, telomeric allelic imbalance and large-scale state transitions from tumor tissue specimens. The results can then be used to guide treatment and therapy for ovarian cancer patients with positive homologous recombination deficiency, which is defined by the presence of *BRCA1/2* mutations and/or positive Genomic Instability Score (Myriad Genetics, 2021).

Clinical Utility and Validity

A study performed by Kuchenbaecker et al. (2017) assessed the cumulative risk of breast and ovarian cancer based on mutation position. A sample of 9856 patients was analyzed, with 6036 patients carrying a *BRCA1* mutation and 3820 with a *BRCA2* mutation. 5046 patients were unaffected by either type of cancer and 4810 had breast cancer, ovarian cancer, or both at baseline. The breast cancer assessment was based on 3886 carriers, and the ovarian cancer assessment was based on 5066 women. The authors evaluated the cumulative risk of breast cancer to 80 years to be 72% for *BRCA1* mutation carriers and 69% for *BRCA2* carriers. Cumulative risk for ovarian cancer to 80 years was found

to be 44% for *BRCA1* carriers and 17% for *BRCA2* carriers. *BRCA2* mutations outside the OCCR were found to have a higher risk of breast cancer than mutations inside it (hazard ratio: 1.93 for OCCR ranges 5' to c.2830, c.2831 to c.6401, c.6402 to 3) but no difference in overall ovarian cancer risk. Mutations closer to the 3' or 5' ends of *BRCA1* were found to have a higher risk of breast cancer compared to the middle third of the gene and the third closest to the 3' end had the highest hazard ratio of 1.51 compared to the third closest to the 5' end (1.43) (Kuchenbaecker et al., 2017).

A meta-analysis of 44 articles was performed to assess the difference in risk factors between *BRCA1* and *BRCA2* carriers. Factors such as breastfeeding, coffee, infertility, and more were examined between both genotypes, and the only risk factor that revealed an association of any kind was age at first live birth for *BRCA1* carriers. Breast cancer risk was found to decrease for *BRCA1* women over 30 compared to women under 30, and the same was found for women from 25-29 compared to women under 25. However, the authors stressed that more research was required (Friebel et al., 2014).

However, the importance of *BRCA* testing has not only been explored for lifestyle choices or transient states; factors such as ethnicity can also play a role in the predisposition of patients to breast cancer. Palmer et al. (2020) delved into the risks of breast cancer in African American (AA) women associated with inherited mutations in breast cancer predisposition genes. Using germline DNA samples and drawing from 10 epidemiologic studies encompassing 5054 affected African American women and 4993 unaffected African American women, Palmer et al. (2020) sequenced mutations in 23 cancer predisposition genes using a QIAseq multiplex amplicon panel and found that pathogenic mutations could be identified in 10.3% of women with estrogen receptor (ER)-negative breast cancer, 5.2% of women with ER-positive breast cancer, and 2.3% of unaffected women. Mutations in *BRCA1*, *BRCA2*, and *PALB2* were associated with an overall increased risk for breast cancer, while *RAD51D* mutations were observed specifically to be linked to higher risk of ER-negative disease. Other mutations the researchers found to be of interest were in *CHEK2*, *ATM*, *ERCC3*, *FANCC,* and *RECQL*. Thus, it was concluded that the study corroborated the use and "validity of current breast cancer testing panels for use in AA women" (Palmer et al., 2020).

A study using next generation sequencing (NGS) to identify *BRCA* mutations was performed by Lang et al. 4034 patients were screened (2991 breast cancer patients, 1043 healthy controls). *BRCA* mutations were found in 247 of the breast cancer patients or 8.3%. 13.9% (16/115) of the *BRCA1* mutations were of the "c.5470_5477del" variation, and several clinical characteristics such as high KI67 index and high tumor grade were related to *BRCA* mutations, *BRCA2* carriers were also found to have poorer disease-free survival among HER2 positive patients (Lang et al., 2017).

Tomao et al. (2019) investigated the ability of *BRCA* mutational status on predicting hematologic toxicity with platinum-based chemotherapy. 176 patients were included, with 58 *BRCA* mutation carriers (40 *BRCA1,* 18 *BRCA2*, 118 controls). The authors identified several differences in hematologic toxicity between the two groups; the *BRCA* positive group was observed to have significantly higher frequency in "thrombocytopenia (24% vs 5%), anemia (21% vs 7%; p = 0.006) and neutropenia (62% vs 27%)". The authors also noted that granulocyte-colony stimulating growth factors injection (12% versus 1%,) and dose delay (19% versus 27%) were more likely in the *BRCA* positive group (odds ratio = 2.567 for granulocyte-colony stimulating growth factors injection and 3.860 for dose delay). Overall,

the authors concluded that "germline *BRCA* ½ mutations are associated with a higher hematologic toxicity in patients with ovarian cancer who underwent platinum-based chemotherapy" (Tomao et al., 2019).

Yoo et al. (2020) conducted *BRCA1/NGS* for 262 hereditary breast and ovarian cancer (HBOC) syndrome patients, and the results were confirmed by using multiplex ligation-dependent probe amplification and direct Sanger sequencing. A multigene panel test was also performed on 120 patients who did not possess *BRCA1/2* pathogenic variants but who met NCCN criteria for testing. The researchers reported that pathogenic variants in *BRCA1/2* were detected in 30 HBOC patients (11.5%), and four out of the 120 patients possessed pathogenic variants of *MSH2 PMS2, CHEK2* and *PALB2*, which were also detectable by multigene panel testing. The results suggested to the authors that "Multi-gene panel testing could be a significant screening tool for HBOC patients, especially for those with a family history of cancer" (Yoo et al., 2020).

BRCA testing has been demonstrated to be potentially beneficial, even when the testing is unselected and is population-based. Manchanda et al. (2020) examined the North London Ashkenazi-Jewish (AJ) population in a randomized controlled trial consisting of 1034 AJ women and men across two arms—one, a population-screening approach, and a second, a family history/clinical-criteria-based *BRCA* testing—to determine subsequent effects on psychological health and quality of life after providing genetic testing for three Jewish *BRCA* founder-mutations. Based on the results of the study, the researchers drew the conclusion that "Population-based AJ *BRCA* testing does not adversely affect long-term psychological wellbeing or quality-of-life, decreases anxiety and could identify up to 150% additional *BRCA* carriers" (Manchanda et al., 2020). However, these results on the anxiety and health-anxiety of this population may be contested, for validated questionnaires were used to measure the psychological wellbeing of the participants at baseline/1-year/2-year/3-year follow-ups. Moreover, the participants were recruited through self-referral, which may affect the internal validity of the trials.

V. Guidelines and Recommendations

National Comprehensive Cancer Network (NCCN)

NCCN guidelines titled *Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Version 3.2023* address general hereditary cancer testing. Note that NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. In this guideline, the terms males and females refer to sex assigned at birth. The NCCN list the following scenarios as "clinically indicated" for genetic testing:

1. "Individual with any blood relative with a known pathogenic/likely pathogen variant in a cancer susceptibility gene" [including *BRCA1/2*]
2. "Individuals meeting the criteria below but tested negative with previous limited testing, (eg, single gene and/or absent deletion duplication analysis) and are interested in pursuing multi-gene testing"
3. "A pathogenic/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"
5. "Individual who meets Li-Fraumeni syndrome (LFS) testing criteria or Cowden syndrome/PTEN

hamartoma tumor syndrome testing criteria or Lynch syndrome"

6. *Personal or family history of cancer*
   a. **Testing for high-penetrance breast cancer susceptibility genes** (Specifically BRCA1, BRCA2, CDH1, PALB2, PTEN, and TP53)**:**
      i. Personal history of breast cancer with specific features:
         a. By Age of diagnosis and family history
            (a) Diagnosed at age ≤50y
            (b) Diagnosed at any age:
            - Treatment indications:
               (i) To aid in systematic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting
               (ii) To aid in adjuvant treatment decisions with Olaparib for high-risk, HER-2 negative breast cancer
            - Pathology/histology:
               (iii) Triple-negative breast cancer
               (iv) multiple primary breast cancers (synchronous or metasynchronous)
               (v) Lobular breast cancer with personal or family history of diffuse gastric cancer
            - Family history:
               (vi) ≥1 close blood relative with ANY:
                  - Breast cancer at age ≤50y
                  - Male breast cancer
                  - Ovarian cancer
                  - Pancreatic cancer
                  - prostate cancer with metastatic[n] or high- or very-high-risk group
               (vii) ≥3 total diagnoses of breast cancer in patient and/or close blood relatives[m]
               (viii) ≥2 close blood relativesm with either breast or prostate cancer (any grade)
            - Ancestry:
               (ix) Ashkenazi Jewish Ancestry
            - Male breast cancer
      ii. Family history of cancer only
         a. An affected individual (not meeting testing criteria listed above) or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).
            - If the affected relative has pancreatic cancer or prostate cancer only first-degree relatives should be offered testing unless indicated based on additional family history.
         b. An affected or unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a BRCA1/2 pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)
   b. **Testing for ovarian cancer susceptibility genes**

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

c. **Testing for pancreatic cancer susceptibility genes**
    i. Exocrine pancreatic cancer
        a. All individuals diagnosed with exocrine pancreatic cancer
        b. First-degree relatives of individuals diagnosed with exocrine pancreatic cancer

d. **Testing for high-penetrance prostate cancer susceptibility genes**
    i. Personal history of prostate cancer with specific features:
        a. By tumor characteristics (any age)
            (a) Metastatic
            (b) Histology
                (i) High- or very-high-risk group
        b. By family history and ancestry
            (a) ≥1 close blood relative with:
                (i) breast cancer at age ≤50 y
                (ii) triple-negative breast cancer at any age
                (iii) male breast cancer at any age
                (iv) ovarian cancer any age
                (v) pancreatic cancer any age
                (vi) metastatic, or high- or very-high risk group at any age
            (b) ≥2 close blood relatives with either breast or prostate cancer (any grade) at any age
            (c) Ashkenazi Jewish ancestry
        c. Family history of cancer only
            (a) An affected (not meeting testing criteria listed above) or unaffected individual with a first-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making)

e. **Testing for Li-Fraumeni Syndrome**
    i. Individual from a family with a known TP53 pathogenic/likely pathogenic variant
    ii. Classic Li-Fraumeni syndrome (LFS) criteria:
        a. Combination of an individual diagnosed at age <45 years with a sarcoma AND
        b. A first-degree relative diagnosed at age <45 years with cancer AND
        c. An additional first- or second-degree relative in the same lineage with cancer diagnosed at age <45 years, or a sarcoma at any age
    iii. Chompret criteria:
        a. Individual with a tumor from LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma), before 46 years of

age, AND at least one first- or second-degree relative with any of the aforementioned cancers (other than breast cancer if the proband has breast cancer) before the age of 56 years or with multiple primaries at any age OR
    b. Individual with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum with the initial cancer occurring before the age of 46 years OR
    c. Individual with adrenocortical carcinoma, or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype, at any age of onset, regardless of family history OR
    d. Breast cancer before 31 years of age
  iv. Pediatric hypodiploid acute lymphoblastic leukemia
  v. Affected individual with pathogenic/likely pathogenic variant identified on tumor genomic testing that may have implications if also identified on germline testing

f. **Testing for Cowden Syndrome (CS)/PTEN Hamartoma Tumor Syndrome (PHTS):**
  i. Individual from a family with a known PTEN pathogenic/likely pathogenic variant
  ii. Individual with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS)
  iii. Individual meeting clinical diagnostic criteria for CS/PHTS
  iv. Individual not meeting clinical diagnostic criteria for CS/PHTS with a personal history of:
    a. Adult Lhermitte-Duclos disease (cerebellar tumors); or
    b. Autism spectrum disorder and macrocephaly; or
    c. Two or more biopsy-proven trichilemmomas; or
    d. Two or more major criteria (one must be macrocephaly); or
    e. Three major criteria, without macrocephaly; or
    f. One major and ≥3 minor criteria; or
    g. 4 minor criteria
  v. At-risk individual with a relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed
    a. The at-risk individual must have the following:
      (a) Any one major criterion or
        (i) Breast cancer
        (ii) Endometrial cancer
        (iii) Follicular thyroid cancer
        (iv) Multiple GI hamartomas or ganglioneuromas
        (v) Macrocephaly (megalocephaly) (ie, ≥97%, 58 cm in adult female, 60 cm in adult male)
        (vi) Macular pigmentation of glans penis
        (vii) Mucocutaneous lesions
          1) One biopsy-proven trichilemmoma
          2) Multiple palmoplantar keratoses
          3) Multifocal or extensive oral mucosal papillomatosis
          4) Multiple cutaneous facial papules (often verrucous)
      (b) Two minor criteria
        (i) Autism spectrum disorder
        (ii) Colon cancer
        (iii) ≥3 esophageal glycogenic acanthoses

(iv) Lipomas
(v) Intellectual disability (ie, IQ ≤75)
(vi) Papillary or follicular variant of papillary thyroid cancer
(vii) Thyroid structural lesions (eg, adenoma, nodule[s], goiter)
(viii) Renal cell carcinoma
(ix) Single GI hamartoma or ganglioneuroma
(x) Testicular lipomatosis
(xi) Vascular anomalies (including multiple intracranial developmental venous anomalies)

vi. PTEN pathogenic/likely pathogenic variant detected by tumor genomic testing on any tumor type in the absence of germline analysis

The NCCN states that general hereditary cancer 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 without additional risk factors.
- Personal history of serious endometrial cancer.

The NCCN states that testing for high-penetrance breast cancer susceptibility genes may be considered in the following scenarios (with appropriate pre-test education and access to post-test management):

1. Personal history of breast cancer < 60 y not meeting any of the above criteria may approach a 2.5% probability of having a PV, based on recent data. It is cautioned that many of those PVs will be in moderate penetrance genes, which are over-represented in older affected individuals, and 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.
2. Personal history of breast cancer diagnosed at any age with ≥1 close blood relative with intermediate-risk prostate cancer with intraductal/cribriform histology.
3. An affected or unaffected individual who otherwise does not meet any of the above criteria but with a 2.5%-5% probability of *BRCA 1/2* pathogenic variant based on prior probability models (e.g. Tyrer-Cuzick, BRCAPro, CanRisk).

The NCCN states that when testing for high-penetrance breast cancer susceptibility genes, there is “a low probability (<2.5%) that testing will have findings of documented high-penetrance genes in the following scenarios:

1. Female diagnosed with breast cancer at age >60 y, with no close relative with breast, ovarian, pancreatic, or prostate cancer
2. Diagnosed with localized prostate cancer with Gleason Score <7 and no close relative with breast, ovarian, pancreatic, or prostate cancer" (NCCN, 2023b).

The NCCN suggests that prior to genetic testing,

- “The probability of pathogenic or likely pathogenic variant detection associated with these criteria will vary based on family structure, which includes size of the family, age of the family members, early death, adoption, and number of male and female relatives. Individuals with unknown or limited family history/structure, such as fewer than 2 female first- or second-degree relatives having lived beyond age 45 in either lineage, may have an underestimated

probability of familial P/LP variant detection. The estimated likelihood of P/LP variant detection may be low in families with many unaffected and/or male relatives.

- Patients who have received an allogeneic bone marrow transplant or with active or recent hematologic malignancies should not have molecular genetic testing via blood, saliva, or buccal samples (due to unreliable test results from contamination by donor DNA) until other technologies are available. If available, DNA should be extracted from a fibroblast culture. If this source of DNA is not possible, buccal samples can be considered, subject to the risk of donor DNA contamination or malignant cells from the hematologic malignancy.
- If more than one family member is affected with cancers highly associated with a particular inherited cancer susceptibility syndrome, consider initial testing of a family member with youngest age at diagnosis, bilateral disease, multiple primary cancers, or other cancers associated with the syndrome, or most closely related to the proband/patient. If there are no available family members with cancer that is a cardinal feature of the syndrome in question, consider testing first- or second-degree family members affected with other cancers thought to be related to the gene in question (eg, prostate or pancreas with *BRCA1/2*).
- Testing for unaffected family members when no affected member is available should be considered. Significant limitations of interpreting test results should be discussed.
- In children <18 y, genetic testing is generally not recommended when results would not impact medical management.
- Likely pathogenic variants are usually clinically managed similarly to pathogenic variants, while patients with variants of uncertain significance (VUS) and likely benign variants should be managed based on the cancers present in the family.
- Choice of multi-gene testing." (NCCN, 2023b)

Furthermore, in the situation where the presence of a pathogenic or likely pathogenic variant is unknown, the NCCN recommends that "the testing of the unaffected individual (or of unaffected family members) should only be considered when no affected family member is available for testing. In such cases, the unaffected individual or unaffected close relative with the highest likelihood of testing positive for the pathogenic or likely pathogenic variant should be tested," though "A negative test result in such cases, however, is considered indeterminate and does not provide the same level of information as when there is known pathogenic or likely pathogenic variant in the family." The NCCN also remarks that "testing multiple family members may be indicated" when testing unaffected individuals "(in the absence of having tested affected family members)" to aid in interpreting results (NCCN, 2023b).

The NCCN also recommends assessing *BRCA1/2* in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy (NCCN, 2023a).
Regarding *BRCA* in ovarian cancer, the NCCN recommends testing for *BRCA1/2* mutations prior to initiating treatment for persistent/recurrent ovarian cancer since "germline and/or somatic *BRCA1/2* status informs maintenance therapy." The NCCN notes that *BRCA* testing may be done prior to this stage (NCCN, 2023c).

BRCA testing was also mentioned in guidelines for pancreatic adenocarcinoma. The NCCN recommends tumor/somatic gene profiling for those with "locally advanced/metastatic disease who

are candidates for anti-cancer therapy to identify uncommon mutations, including testing for mutations in *BRAF, BRCA1/2, HER2, KRAS,* and *PALB2* genes, fusions in *ALK, NRG1, NTRK, ROS1, FGFR2, RET* genes, microsatellite instability (MSI), mismatch repair deficiency *(dMMR*) , or tumor mutational burden (TMB) via an FDA-approved and/or validated next-generation sequencing (NGS)- based assay" (NCCN, 2023d).

The NCCN also published guidelines regarding *BRCA* in prostate cancer. Germline genetic testing, which should include *BRCA1/2* among other genes, such as *ATM, PALB2,* and *CHEK2* was recommended for initial patients with prostate cancer and any of the following: "a positive family history; high-risk, very-high-risk, regional, or metastatic prostate cancer, regardless of family history; Ashkenazi Jewish ancestry; [and] a personal history of breast cancer." The NCCN also notes that "germline genetic testing should be considered in patients with a personal history of prostate cancer and 1) intermediate-risk prostate cancer and intraductal/cribriform histology or 2) a personal history of exocrine pancreatic cancer, breast cancer, colorectal, gastric, melanoma, pancreatic cancer, upper tract urothelial cancer, glioblastoma, biliary tract cancer, and small intestinal cancer" Moreover, the NCCN asserts that germline testing should include "*MLH1, MSH2, MSH6, and PMS2* (for Lynch syndrome) and homologous recombination genes *BRCA1, BRCA2, ATM, PALB2, and CHEK2*", urging that cancer predisposition next-generation sequencing be considered (NCCN, 2023e).
Regarding somatic tumor testing in risk groups,

- "Tumor testing for somatic homologous recombination gene mutations (eg, *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, CDK12*) can be considered in patients with regional (N1) prostate cancer and is recommended for those with metastatic disease.
- Tumor testing for MSI or dMMR can be considered in patients with regional or metastatic castration-naïve prostate cancer and is recommended in the metastatic castrate-resistant prostate cancer (CRPC) setting.
- Tumor mutational burden (TMB) testing may be considered in patients with metastatic CRPC.
- Multigene molecular testing can be considered for patients with low-, intermediate-, and high-risk prostate cancer and life expectancy ≥10 years.
- The Decipher molecular assay is recommended to inform adjuvant treatment if adverse features are found post-radical prostatectomy and can be considered as part of counseling for risk stratification in patients with PSA resistance/recurrence after radical prostatectomy (category 2B)." (NCCN, 2023e)

The NCCN published information on *TP53* as a pathogenic/likely pathogenic variant, noting that testing for Li-Fraumeni syndrome should occur when the individual is from a family with a known *TP53* pathogenic/likely pathogenic variant. They specifically note that when this gene is "included as part of a multi-gene panel, an individual does not need to meet these testing criteria [for Li-Fraumeni syndrome]- if "testing criteria on other testing criteria pages are met" (NCCN, 2023b).

The U.S. Preventive Services Task Force (USPSTF)
In 2019, the USPSTF updated their 2014 recommendation (Moyer, 2014). In it, they state that "the USPSTF recommends that primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with breast cancer susceptibility 1 and 2 (*BRCA1*/2) gene mutations with an appropriate brief familial risk assessment tool.

Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing." This recommendation is intended for women with a "personal or family history of breast, ovarian, tubal, or peritoneal cancer or an ancestry associated with *BRCA1*/2 gene mutation" (USPSTF, 2019).
Moreover, they do not recommend (i.e. issue a D recommendation) routine screening, genetic testing, or genetic counseling for women who have no family or personal history of breast cancer or whose ancestry or ethnicity is not associated with a higher risk for potentially pathogenic *BRCA1* or *BRCA2* gene mutations (USPSTF, 2019).

The American College of Obstetricians and Gynecologists (ACOG)
The ACOG released guidelines in 2019 for Hereditary Cancer Syndromes and Risk Assessments. The ACOG recommends:

- Evaluating a patient's risk of hereditary breast and ovarian cancer syndrome should be a routine part of obstetric and gynecologic practice. Initial risk evaluation should include a personal medical history and family history.
- Genetic testing is recommended when the results of a detailed risk assessment that is performed as part of genetic counseling suggest the presence of an inherited cancer syndrome for which specific genes have been identified and when the results of testing are likely to influence medical management.
- The two main genetic testing options for hereditary breast and ovarian cancer syndrome are *BRCA* mutation testing and multigene panel testing that includes both *BRCA* and other genetic mutations. Multigene panel testing may be useful when more than one gene may be associated with an inherited cancer syndrome or when a patient has a personal or family history that is consistent with an inherited cancer susceptibility, but single-gene testing has not identified a pathogenic variant (ACOG, 2019).

The American Society of Breast Surgeons (ASBS)
The American Society of Breast Surgeons have released guidelines on genetic testing for hereditary breast cancer. They are as follows:

1. "Breast surgeons, genetic counselors, and other medical professionals knowledgeable in genetic testing can provide patient education and counseling and make recommendations to their patients regarding genetic testing and arrange testing"
2. "Genetic testing should be made available to all patients with a personal history of breast cancer. Recent data support that genetic testing should be offered to each patient with breast cancer (newly diagnosed or with a personal history). If genetic testing is performed, such testing should include *BRCA1*/*BRCA2* and *PALB2*, with other genes as appropriate for the clinical scenario and family history. For patients with newly diagnosed breast cancer, identification of a mutation may impact local treatment"
3. "Patients who had genetic testing previously may benefit from updated testing. Every patient being seen by a breast surgeon, who had genetic testing in the past and no pathogenic variant was identified, should be re-evaluated and updated testing considered. In particular, a patient who had negative germline *BRCA1* and 2 testing, who is from a family with no pathogenic variants, should be considered for additional testing.1 Genetic testing performed prior to 2014 most likely would not have had PALB2 or other potentially relevant genes included and may not

have included testing for large genomic rearrangements in *BRCA1* or *BRCA2*"

4. "Genetic testing should be made available to patients without a history of breast cancer who meet NCCN guidelines. Unaffected patients should be informed that testing an affected relative first, whenever possible, is more informative than undergoing testing themselves. When it is not feasible to test the affected relative first, then the unaffected family member should be considered for testing if they are interested, with careful pre-test counseling to explain the limited value of "uninformative negative" results. It is also reasonable to order a multi-gene panel if the family history is incomplete (i.e., a case of adoption, patient is uncertain of exact type of cancer affecting family members, among others) or other cancers are found in the family history, as described above" (Manahan et al., 2019).

American Society of Clinical Oncology (ASCO)

ASCO recommends germline genetic testing for *BRCA1/2* for all women diagnosed with epithelial ovarian cancer. Somatic tumor testing for *BRCA1/2* should be performed in women that do not carry a germline pathogenic or likely pathogenic variant (Konstantinopoulos et al., 2020).

ASCO also published a guideline regarding PARP inhibitors for ovarian cancer. In recommendation 2.2, they recommend the use of "Myriad myChoice CDx" to determine *BRCA1/2* status for therapy decisions (Tew et al., 2020).

National Institute for Health and Care Excellence

NICE updated their guidelines on familial breast cancer in 2019. In it, they maintain their *BRCA*-related recommendations from 2013, which are as follows:

"Offer genetic testing in specialist genetic clinics to a relative with a personal history of breast and/or ovarian cancer if that relative has a combined *BRCA1* and *BRCA2* mutation carrier probability of 10% or more."

"Offer genetic testing in specialist genetic clinics to a person with no personal history of breast or ovarian cancer if their combined *BRCA1* and *BRCA2* mutation carrier probability is 10% or more and an affected relative is unavailable for testing."

"Offer genetic testing in specialist genetic clinics to a person with breast or ovarian cancer if their combined *BRCA1* and *BRCA2* mutation carrier probability is 10% or more" (NICE, 2019).

European Expert Group

A group of 19 experts in *BRCA* testing were convened to publish this set of guidelines. These experts came from across Europe and Israel, and participants included clinical or medical geneticists (32%), oncologists (37%), and gynaecologists (26%).

The guidelines state that with the rise of next-generation sequencing, hotspot testing instead of complete sequencing is "not acceptable", albeit noting a possible exception of founder mutations representing >99% of pathogenic variants in a specific area.

A majority of experts (60%) voted that *BRCA* testing should be offered to all patients with metastatic breast cancer (Singer et al., 2019).

VI. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration

The Center for Devices and Radiological Health of the Food and Drug Administration (FDA, 2018) granted premarket approval on 1/12/2018 to BRACAnalysis CDx® is an in vitro diagnostic device intended for the qualitative detection and classification of variants in the protein coding regions and intron/exon boundaries of the *BRCA1* and *BRCA2* genes using genomic DNA obtained from whole blood specimens collected in EDTA. Single nucleotide variants and small insertions and deletions (indels) are identified by polymerase chain reaction (PCR) and Sanger sequencing. Large deletions and duplications in *BRCA1* and *BRCA2* are detected using multiplex PCR. Another FDA-approved device is the "FoundationFocus CDxBRCA", which is a "is a next generation sequencing based in vitro diagnostic device for qualitative detection of *BRCA1* and *BRCA2* alterations in formalin-fixed paraffin-embedded (FFPE) ovarian tumor tissue". This test is intended to be used "as an aid in identifying ovarian cancer patients for whom treatment with Rubraca (rucaparib) is being considered" (FDA, 2016). A more recent FDA-approved device comes out of Myriad Genetics, Inc., the myChoice HRD CDx, which was approved on October 23, 2019. This test is a "next generation sequencing-based in vitro diagnostic test that assesses the qualitative detection and classification of single nucleotide variants, insertions and deletions, and large rearrangement variants in protein coding regions and intron/exon boundaries of the BRCA1 and BRCA2 genes and the determination of Genomic Instability Score (GIS)" based off tumor tissue specimens.

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status.

HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VIII. Evidence-based Scientific References

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IX. Policy History

Action Date	Action
06/01/2023	Initial policy implementation
11/21/2023	Policy approved by Medical Directors
12/15/2023	Policy approved at UMC
2/01/2025	Policy effective date following notification period