


<b>MEDICAL POLICY</b>	<b>Genetic Testing: Hereditary Breast and Ovarian Cancer(All Lines of Business Except Medicare)</b>
<b>Effective Date: 08/01/2021</b>	Medical Policy Number: 143
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Medical Officer	Date

**See Policy CPT CODE section below for any prior authorization requirements**

**SCOPE:**

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

**APPLIES TO:**

All lines of business except Medicare

**BENEFIT APPLICATION**

Medicaid Members

*Oregon:* Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

**POLICY CRITERIA**

Notes:

- This policy does not address pharmacogenetic testing for hereditary breast and ovarian cancer. Please see Genetic Testing: Pharmacogenetic Testing (All Lines of Business except Medicare).
- Non-covered genetic testing panels related to hereditary breast and ovarian cancer are addressed in our Genetic Testing: Non-Covered Genetic Panel Tests (All Lines of Business Except Medicare) policy. Please see policy for complete list of panels.
- Both maternal and paternal family histories must be considered separately when identifying families with an increased risk of breast and/or ovarian cancer.

**Policy Criteria Links**

- [Genetic Counseling](#)
- [Genetic Testing: Family with a Known Breast and/or Ovarian Cancer Mutation](#)
- [Genetic Testing: Personal History of Cancer](#)
- [Genetic Testing: No Personal History of Cancer](#)
- [Genetic Testing: Non-Covered Testing](#)

**Genetic Counseling**

- I. The following genetic counseling criteria must be met prior to testing of any one or more [breast and/or ovarian cancer gene mutations](#):
  - A. Provider meets current NCCN guidelines as a [certified genetic counselor or board-certified physician](#) trained in cancer genetics; **and**
  - B. A full personal and family history, which includes first-, second-, and third-degree pedigree, has been conducted and is documented; **and**
  - C. Genetic testing information and pre-test counseling has been provided and is documented; **and**
  - D. Patient has undergone and signed informed consent for genetic testing; **and**
  - E. Post-test counseling to review the test results and determine future medical management and treatment plans has been discussed and will be scheduled.

**Genetic Testing: Family with a Known Breast and/or Ovarian Cancer Mutation**

- II. Genetic testing for a [hereditary breast and/or ovarian cancer gene mutation](#) may be considered **medically necessary and covered** when **all** of the following criteria (A-C) are met:
  - A. Genetic Counseling criterion I. above, is met; **and**
  - B. The patient is from a family with a known pathogenic/likely pathogenic variant in a [hereditary breast and/or ovarian cancer gene](#); **and**
  - C. Gene testing is specific to the familial pathogenic/likely pathogenic variant.

**Genetic Testing: Personal History of Cancer**

- III. Genetic testing for [hereditary breast and/or ovarian cancer gene mutation\(s\)](#) may be considered **medically necessary and covered** when **both** of the following criteria (A. and B.) are met:

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- A. Genetic Counseling criterion I. above, is met; **and**
- B. Any **one or more** of the following criteria (1.-7.) are met:
1. The patient has a personal history of breast cancer (including invasive and ductal carcinoma *in situ*) and any **one or more** of the following criteria (a.-e.) are met:
    - a. Diagnosed with breast cancer at age 45 or younger; **or**
    - b. Diagnosed with breast cancer at age 46-50 with **any** of the following:
      - i. Two breast primaries diagnosed at any age (includes bilateral [contralateral] disease or cases where there are two or more clearly separated [ipsilateral] primary tumors either synchronously or asynchronously); **or**
      - ii. 1 or more [close blood relative](#) with breast cancer at any age; **or**
      - iii. 1 or more [close blood relative](#) with high grade (Gleason score  $\geq 7$ ) prostate cancer; **or**
    - c. Diagnosed with breast cancer at age 60 or younger and triple negative breast cancer (breast cancer cells have tested negative for hormone epidermal growth factor receptor 2 [HER-2], estrogen receptors [ER], and progesterone receptors [PR]); **or**
    - d. Diagnosed with breast cancer **at any age and any one** of the following criteria are met:
      - i. 1 or more [close blood relative](#) with **any** of the following:
        - breast cancer at age 50 or younger; **or**
        - invasive ovarian cancer (including fallopian tube or primary peritoneal cancer) at any age; **or**
        - male breast cancer; or pancreatic cancer; **or**
        - high grade (Gleason score  $\geq 7$ ) or metastatic prostate cancer (biopsy-proven and/or with radiologic evidence and includes distant metastases and regional bed or nodes); **or**
      - ii. A known pathogenic/likely pathogenic variant in a [hereditary breast and/or ovarian cancer gene](#) is known in the family;
      - iii. 2 or more [close blood relatives](#) with breast cancer at any age; **or**
      - iv. Personal history of pancreatic cancer at any age;
      - v. Ethnicity associated with higher mutation frequency or increased risk of founder mutation (e.g., Ashkenazi Jewish, Norwegian, Dutch, or Icelander descent); **or**
      - vi. Patient has a limited family history; **or**
- Note: A limited family history occurs when a 1st, 2nd and 3rd generation pedigree cannot be obtained or when there are too few family members in each generation to reasonably see a pattern of inheritance.

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2. The patient has ovarian cancer (includes fallopian tube and primary peritoneal cancers); **or**
3. The patient has male breast cancer; **or**
4. The patient has pancreatic cancer; **or**
5. The patient has metastatic prostate cancer (biopsy-proven and/or with radiologic evidence and includes distant metastases and regional bed or nodes); **or**
6. The patient has high-grade (Gleason score  $\geq 7$ ) prostate cancer at any age with **any** of the following:
  - a. 1 or more [close blood relative](#) with any of the following:
    - i. breast cancer at age 50 or younger; **or**
    - ii. invasive ovarian cancer (including fallopian tube or primary peritoneal cancer) at any age; **or**
    - iii. pancreatic cancer at any age; **or**
    - iv. metastatic prostate cancer at any age (biopsy-proven and/or with radiologic evidence and includes distant metastases and regional bed or nodes); **or**
  - b. Is of Ashkenazi Jewish decent; **or**
7. The patient has a personal and/or family history of **3 or more** of the following diagnosis (can include multiple primary cancers in the same individual):
  - a. Breast cancer
  - b. Pancreatic cancer
  - c. Prostate cancer (Gleason score  $\geq 7$  or metastatic)
  - d. Melanoma
  - e. Sarcoma
  - f. Adrenocortical carcinoma
  - g. Brain tumors
  - h. Leukemia
  - i. Diffuse gastric cancer
  - j. Colon cancer
  - k. Endometrial cancer
  - l. Thyroid cancer
  - m. Kidney cancer
  - n. [Dermatological manifestations](#) of Cowden syndrome
  - o. Macrocephaly
  - p. Gastrointestinal cancer or hamartomatous polyps of GI tract
  - q. Ovarian sex chord tumors
  - r. Testicular sertoli cell tumors
  - s. [Childhood skin pigmentation](#) indicative of Peutz-Jeghers syndrome

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8. A known pathogenic/likely pathogenic variant in a [hereditary breast and/or ovarian cancer gene](#) detected by tumor profiling on any tumor type in the absence of germline variant analysis.

**Genetic Testing: No Personal History of Cancer**

- IV. Genetic testing for [hereditary breast and/or ovarian cancer gene mutation\(s\)](#) may be considered **medically necessary and covered** when the Genetic Counseling criterion I. above is met **and** any one or more of the following criteria (A or B) are met:
- A. The patient has a first- or second- degree blood relative who meets criterion III.B. above; **or**
  - B. The patient has a first- or second- degree blood relative with at least two [close blood relatives](#) with breast cancer primaries on the same side of the family with at least one diagnosed at age 50 or younger.

**Notes:**

- Criterion IV. may apply to an affected third-degree relative if related through two male relatives (e.g., paternal grandfather's mother or sister).
- When possible, family members with cancer associated with inherited breast and/or ovarian cancer should be tested first, prior to testing unaffected members. Documentation that testing an unaffected member has significant limitations on interpreting test results. Pre-test counseling notes should document the reason why none of these members can be tested prior to testing an unaffected member.

**Genetic Testing: Non-covered Testing**

- V. Initial or repeat genetic testing for [hereditary breast and/or ovarian cancer gene mutation\(s\)](#) is considered **not medically necessary and is not covered** when any of the criteria (I.-IV.) above is not met.
- VI. Genetic testing for [hereditary breast and/or ovarian cancer gene mutation\(s\)](#) is considered **investigational and is not covered** in patients who have received an allogeneic bone marrow transplant if only blood or buccal samples are available. Fibroblast culture is the only acceptable source of DNA for these patients.

**Note:** Per the NCCN, testing from blood and buccal sources may be unreliable due to donor-derived DNA.<sup>1</sup>

Link to [Policy Summary](#)

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**POLICY GUIDELINES**

Hereditary Breast and/or Ovarian Cancer Gene Mutations

The following genes are associated with an increased risk of breast and/or ovarian cancer:<sup>1</sup>

- ATM
- BRCA1
- BRCA2
- BRIP1
- CDH1
- CHEK2
- EPCAM
- MLH1
- MSH2
- MSH6
- NBN
- NF1
- PALB2
- PMS2
- PTEN
- RAD51C
- RAD51D
- STK11
- TP53

Note: BART testing for large rearrangements (e.g., large deletions and/or duplications) may be included and is covered as a component of BRCA 1 and/or 2 testing when medical necessity criteria are met.

*Genetic Panel Testing*

The clinical utility of testing has been established for all 19 of the genes listed above. Therefore, when medical necessity criteria are met, genetic panel testing for hereditary breast and ovarian cancer risk may include one or more of **any combination** of the genes listed in this section above. For example, genetic panels, such as the INVITAE Hereditary Breast and Ovarian Cancer Syndrome Panel, which only include select genes from the list above, may be considered medically necessary when criteria are met.

Genetic Counseling Requirements

Genetic studies and counseling are approved subject to benefits when there is a medical condition that requires genetic counseling and potential subsequent testing to diagnose or to aide in planning a treatment course. Identification of a genetic disorder should result in medical and/or surgical management that is corrective and/or therapeutic in nature.

Prior to authorization of a genetic test, and in accordance with National Comprehensive Cancer Network guidelines, the member must have undergone pretest counseling by a certified genetic counselor or a provider trained in cancer genetics. A provider trained in cancer genetics is defined as providing cancer risk assessment on a regular basis and having received specialized ongoing training in cancer genetics. Education limited to learning how to order a test is not considered adequate training for cancer risk assessment and genetic counseling. The provider may be required to provide documentation of genetic training and ongoing continual medical education (CME). Examples of providers trained in genetic counseling are:

- Board-Eligible or Board-Certified Genetic Counselor (CGC)
- Advanced Genetics Nurse (AGN-BC), Genetic Clinical Nurse (GCN)
- Advanced Practice Nurse in Genetics (APNG)
- Board-Eligible or Board-Certified Clinical Geneticist

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- Board-Certified Physician with training and ongoing experience in cancer genetics (e.g., surgical oncologist, medical oncologist, fellowship-trained breast surgeon, OBGYN)

The genetic counseling visit is expected to encompass the following:

1. Pretest counseling documenting:
  - Comprehensive family history/pedigree which includes first-, second- and third-degree relatives on both maternal and paternal side of the family; and
  - Evaluation of a patients cancer risk; and
  - A differential diagnosis and documentation of having educated the member on inheritance patterns, penetrance, variable expressivity and the possibility of genetic heterogeneity; and
  - Documentation that the member has been prepared for possible outcomes of testing including positive, negative and uncertain findings; and
  - When possible, family members with cancer associated with inherited breast and/or ovarian cancer should be tested first, prior to testing unaffected members.
    - Documentation that testing an unaffected member has significant limitations on interpreting test results. Pre-test counseling note should document the reason why none of these members can be tested prior to testing an unaffected member; and
  - Informed consent for genetic testing was obtained.
2. Posttest counseling will be scheduled and expected to provide the following:
  - Results along with their significance and impact and recommended medical and/or surgical management options; and
  - Interpretation of results in context of personal and family history of cancer; and
  - Informing and recommending testing of at-risk family members; and
  - Providing available resources such as disease-specific support groups and research studies; and
  - Appropriate referral to medical specialties to assist with long term medical management and risk reduction strategies
  - If a mutation is found, post-test counseling will include not only the affected member but recommendations regarding inherited risk to relatives and options for risk assessment and management
  - If a mutation is found in a patient of reproductive age, post-test counseling will also include reproductive decision-making and/or risk assessment and management.

#### Close Blood Relatives

The National Comprehensive Cancer Network (NCCN) defines close blood relative as first- (parents, siblings and children), second- (grandparents, aunts, uncles, nieces and nephews, grandchildren and half-siblings), and third degree-relatives (great-grandparents, great-aunts, great uncles, great grandchildren and first cousins) on same side of family.<sup>1</sup>

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Dermatological manifestations

For a complete list of dermatological manifestations of Cowden syndrome, please see the current NCCN guidelines on [“Genetic/Familial High-Risk Assessment: Breast and Ovarian.”](#)<sup>1</sup>

Childhood Skin Pigmentation Indications

For a complete list of childhood skin pigmentation indicative of Peutz-Jeghers syndrome, please see the current NCCN guidelines on [“Genetic/Familial High-Risk Assessment: Colorectal.”](#)<sup>2</sup>

**BILLING GUIDELINES**

BART testing for large rearrangements (e.g., large deletions and/or duplications), billed with 81164 **OR** 81166 and/or 81167, may be denied as not covered when the medical necessity for hereditary breast or ovarian cancer testing (above) is not met.

When no specific CPT or HCPCS code exists for the panel, the provider is required to bill using an unlisted code. It is not appropriate for the provider to bill any of the tests in a panel separately as if they were performed individually. This is a misrepresentation of services performed and is not appropriate based on either CPT or CMS guidelines. In a “Healthcare Fraud Prevention Partnership” white paper published in May, 2018, CMS identified unbundling of lab panels as an example of fraudulent billing.

**CPT CODES**

Genetic testing for hereditary breast and/or ovarian cancer may include but is not limited to any of the CPT codes listed below. Additional codes may apply.

All Lines of Business Except Medicare	
Prior Authorization Required	
0129U	Hereditary breast cancer–related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53)
0137U	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) mRNA sequence analysis (List separately in addition to code for primary procedure)
0138U	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) mRNA sequence analysis (List separately in addition to code for primary procedure)
0238U	Oncology (Lynch syndrome), genomic DNA sequence analysis of MLH1, MSH2, MSH6, PMS2, and EPCAM, including small sequence changes in exonic and intronic regions,



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	deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
81162	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis
81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81165	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81212	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
81215	BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81216	BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81217	BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81293	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81294	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81296	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81297	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81298	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81299	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81300	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81307	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; full gene sequence

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81308	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; known familial variant
81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81322	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
81323	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
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 14 genes, including ATM, BRCA1, BRCA2, BRIP1, CDH1, MLH1, MSH2, MSH6, NBN, PALB2, PTEN, RAD51C, 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
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis and RNA analysis when performed, 5-50 genes (EG, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
81455	Targeted genomic sequence analysis panel, solid organ or hemtolympoid neoplasm , DNA analysis and RNA analysis when performed, 51 or greater genes (EG, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
<b>No Prior Authorization Required</b>	
81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)

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81166	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81167	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
<b>Unlisted Codes</b> All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then <b>prior-authorization is required.</b>	
81479	Unlisted molecular pathology procedure

**DESCRIPTION**

Clinical Utility of Genetic Testing

Establishing the clinical utility of any test is a key component in determining its ultimate usefulness. Clinical utility may be established when published evidence demonstrates test results can be used to:

1. Guide treatment, management, or preventive decisions; and
2. Those decisions lead to improved primary health outcomes.

Genetic Panel Testing

Numerous genetic panels are available which test for various combinations of genes associated with hereditary breast and/or ovarian cancer. Some well-designed genetic panel tests include only the genes which have demonstrated clinical utility and high penetrance. However, other panel tests include a broader range of genes for which penetrance levels are intermediate and low and the clinical utility of testing is not yet established. It is not recommended that patients undergo testing for gene mutations with unknown clinical significance as test results may lead to unnecessary interventions and additional testing which is not supported by current evidence or practice standards. Therefore, the clinical utility of each gene included in the panel must be demonstrated in order to establish the medical necessity of the panel test.

**REVIEW OF EVIDENCE**

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of genetic testing for hereditary breast and ovarian cancer. Below is a summary of the available evidence identified through March 2021.

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Genetic Testing: Personal History of Cancer

In 2016 (updated 2020), Hayes conducted a systematic review evaluating the clinical utility of genetic testing for hereditary breast and ovarian cancer (HBOC) in patients with a personal history and a suggestive family history of cancer.<sup>3</sup> In total, 1159 abstracts were examined, 289 studies were identified for further review, and 24 studies were included for detailed review. Sample size ranged from 26 to 9,982. Genetic tests for *BRCA1*, *BRCA2*, or other genes associated with HBOC syndromes were used as index tests, with comparison to *BRCA* ½ status and HBOC status. Outcomes of interest included diagnostic yield, survival, disease progression, uptake of counseling, testing, surveillance/screening methods, and impact on family members.

Overall, studies indicated that genetic testing of an affected individual is clinically useful, capable of leading to changes in patient management, diagnostic thinking about the hereditary cancer syndrome diagnosis and in the clinical management of at-risk relatives. Genetic testing was also found to inform prognosis and/or predict response to treatment for patients with HBOC. The overall quality of evidence was determined to be “moderate”, comprising 11 “very poor- to poor-quality” studies and 13 “fair quality” studies. Limitations included studies’ retrospective design, small sample sizes, statistical weaknesses, and failure to adjust for potential confounders in analyses.

Hayes ultimately assigned an “A” rating (established benefit) for genetic testing of germline variants in patients with a personal history of breast and/or ovarian cancer and a family history suggestive of HBOC. Investigators noted testing’s ability to reduce subsequent cancer risk through surveillance and risk-reducing procedures, identify variants associated with treatment response, identify at-risk family members, and “balanc[e] this with current limitations such as incomplete scientific understanding of pathogenic variants in specific patient populations.”<sup>3</sup>

Genetic Testing: No Personal History of Cancer

In 2016 (updated 2020), Hayes conducted a systematic review evaluating the clinical utility of genetic testing for hereditary breast and ovarian cancer (HBOC) in patients with no personal history and a suggestive family history of cancer.<sup>4</sup> In total, 11 studies were included for detailed review. Sample size ranged from 26 to 2,509 unaffected/asymptomatic individuals with a family history suspected of, or confirmed to be at risk for HBOC. Genetic tests for *BRCA1*, *BRCA2*, other genes associated with hereditary cancer syndromes were employed as index tests; *BRCA1/2* status, HBOC status, study setting, insurance status were used as comparators. Outcomes of interest included the incidence of pathogenic variant(s); recommendation for and uptake of counseling/testing. Screening, prophylactic procedures and psychological impact.

Overall, studies indicated that genetic testing of an unaffected individual can lead to a change in patient management, informing clinical management strategies (e.g., surveillance strategies, prophylactic measures) that would otherwise have been missed by testing only 1 or 2 genes (e.g., *BRCA1/2*). Testing also conferred eligibility for prophylactic procedures, and was informative for family members, who subsequently became eligible for genetic counseling/testing, increased disease surveillance, and/or

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prophylactic procedures. The overall quality of evidence was determined to be “moderate,” with study quality ranging from “poor” to “fair.” Limitations included studies’ retrospective design, small sample size, survival bias, and insufficient reporting of methods, statistical analysis and results. Despite limitations, Hayes ultimately assigned a “B” rating (some proven benefit) for genetic testing of patients who are unaffected/asymptomatic with a family history of HBOC syndrome.

Genetic Testing: Non-Covered Testing

In 2016 (retired 2020), Hayes conducted a systematic review evaluating the evidence base of the myRisk Hereditary Cancer (Myriad) genetic test.<sup>5</sup> The panel examines 25 genes using next-generation sequencing (NGS) technology combined with patient clinical factors to assess cancer risk. In total, 3 studies were included for review – 1 analytical validity study and 2 studies that assess the 25-gene panel. No evidence basis was identified supporting the use of the myRisk test due to a lack of evidence. Hayes assigned a “D2” rating (insufficient evidence) for the myRisk Hereditary Cancer test due to a lack of research reporting improvements in patient care, and/or informing patients of familial elevated risk for cancer. Investigators called for additional studies assessing analytical and clinical validity and clinical utility to demonstrate the test’s benefit.

**CLINICAL PRACTICE GUIDELINES**

The medical necessity criteria within this policy are primarily supported and guided by the National Comprehensive Cancer Network Genetic/Familial High-Risk Assessment: Breast and Ovarian clinical practice guidelines.<sup>1</sup>

National Comprehensive Cancer Network (NCCN)

The November 2020 NCCN guidelines regarding hereditary assessment for breast and ovarian cancer recommend the following:<sup>1</sup>

<b>NCCN GUIDELINES Breast and Ovarian Management Based On Genetic Test Results</b>		
<b>Gene</b>	<b>Breast Cancer Risk Management</b>	<b>Ovarian Cancer Risk Management</b>
<i>ATM</i>	<u>Increased Risk of Breast Cancer</u> <ul style="list-style-type: none"> <li>• Screening: Annual mammogram and consider tomosynthesis and breast MRI with contrast starting at age 40 years.</li> <li>• Risk-reducing mastectomy: Consider based on family history.</li> </ul>	Risk-reducing RRSO: Manage based on family history.
<i>BARD1</i>	<ul style="list-style-type: none"> <li>• Screening: Annual mammogram with consideration of tomosynthesis and</li> </ul>	no evidence for increased risk

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	<p>breast MRI with contrast starting at age 40 years.</p> <ul style="list-style-type: none"> <li>Risk-reducing mastectomy: consider based on family history.</li> </ul>	
<i>BRCA1</i>	<p><u>Increased Risk of Breast Cancer</u></p> <ul style="list-style-type: none"> <li>See NCCN guidelines regarding BRCA Pathogenic Variant-Positive Management<sup>1</sup></li> </ul>	<p><u>Increased Risk of Ovarian Cancer</u></p> <ul style="list-style-type: none"> <li>See NCCN guidelines regarding BRCA Pathogenic Variant--Positive Management<sup>1</sup></li> </ul>
<i>BRCA2</i>	<p><u>Increased Risk of Breast Cancer</u></p> <ul style="list-style-type: none"> <li>See NCCN guidelines regarding BRCA Pathogenic Variant-Positive Management<sup>1</sup></li> </ul>	<p><u>Increased Risk of Ovarian Cancer</u></p> <ul style="list-style-type: none"> <li>See NCCN guidelines regarding BRCA Pathogenic Variant-Positive Management<sup>1</sup></li> </ul>
<i>BRIP1</i>	<p>Potential increase in female breast cancer (including triple negative) risk with insufficient evidence for risk management</p>	<p><u>Increased Risk of Ovarian Cancer</u></p> <ul style="list-style-type: none"> <li>Consider risk-reducing salpingo-oophorectomy at 45-50 years.</li> </ul>
<i>CDH1</i>	<p><u>Increased Risk of Lobular Breast Cancer</u></p> <ul style="list-style-type: none"> <li>Screening: Annual mammogram and consider tomosynthesis and breast MRI with contrast starting at age 30 years.</li> <li>Risk-reducing mastectomy: Consider based on family history.</li> </ul>	<p>No increased risk of ovarian cancer</p>
<i>CDKN2A</i>	<p>No increased risk of breast cancer</p>	<p>No increased risk of ovarian cancer</p>
<i>CHEK2</i>	<p><u>Increased Risk of Breast Cancer</u></p> <ul style="list-style-type: none"> <li>Screening: Annual mammogram and consider tomosynthesis and breast MRI with contrast age 40 years.</li> <li>Risk-reducing mastectomy: Evidence insufficient, manage based on family history.</li> </ul>	<p>No increased risk of ovarian cancer</p>
<i>MSH2, MLH1, MSH6, PMS2, EPCAM</i>	<p>Unknown or insufficient evidence for breast cancer risk. Manage based on family history.</p>	<p><u>Increased Risk of Ovarian Cancer</u></p> <ul style="list-style-type: none"> <li>See NCCN guidelines for Genetic/Familial High-Risk Assessment: Colorectal<sup>2</sup></li> </ul>
<i>NBN</i>	<p><u>Increased Risk of Breast Cancer for individuals with 657del5 variant</u></p> <ul style="list-style-type: none"> <li>Screening: Annual mammogram and consider tomosynthesis and breast MRI with contrast age 40 years.</li> <li>Risk-reducing mastectomy: Evidence insufficient, manage based on family history.</li> </ul>	<p><u>Potential increase in ovarian cancer risk</u></p> <ul style="list-style-type: none"> <li>Consider risk-reducing salpingo-oophorectomy based on family history</li> </ul>

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<i>NF1</i>	<u>Increased Risk of Breast Cancer</u> <ul style="list-style-type: none"> <li>Screening: Annual mammogram starting at age 30 yrs and consider tomosynthesis and breast MRI with contrast from ages 30-50 years.</li> <li>Risk-reducing mastectomy: Evidence insufficient, manage based on family history.</li> </ul>	No increased risk of ovarian cancer
<i>PALB2</i>	<u>Increased Risk of Breast Cancer</u> <ul style="list-style-type: none"> <li>Screening: Annual mammogram and consider tomosynthesis and breast MRI with contrast age 30 years.</li> <li>Risk-reducing mastectomy: Consider based on family history.</li> </ul>	<u>Potential increase in ovarian cancer risk</u> <ul style="list-style-type: none"> <li>Consider risk-reducing salpingo-oophorectomy based on family history, evidence insufficient</li> </ul>
<i>PTEN</i>	<u>Increased Risk of Breast Cancer</u> <ul style="list-style-type: none"> <li>See the NCCN guidelines regarding Cowden Syndrome management</li> </ul>	No increased risk of ovarian cancer
<i>RAD51C</i>	Potential increase in triple-negative female breast cancer risk with insufficient evidence for risk management, manage based on family history	<u>Increased Risk of Ovarian Cancer</u> <ul style="list-style-type: none"> <li>Consider risk-reducing salpingo-oophorectomy at 45-50 years.</li> </ul>
<i>RAD51D</i>	Potential increase in triple-negative female breast cancer risk with insufficient evidence for risk management, manage based on family history	<u>Increased Risk of Ovarian Cancer</u> <ul style="list-style-type: none"> <li>Consider risk-reducing salpingo-oophorectomy at 45-50 years.</li> </ul>
<i>STK11</i>	<u>Increased Risk of Breast Cancer</u> <ul style="list-style-type: none"> <li>Screening: See NCCN guidelines for Genetic/Familial High-Risk Assessment: Colorectal<sup>2</sup> – Peutz-Jeghers syndrome</li> <li>Risk-reducing mastectomy: Evidence insufficient, manage based on family history.</li> </ul>	<u>Increased Risk of Non-epithelial Ovarian Cancer</u> See NCCN guidelines for Genetic/Familial High-Risk Assessment: Colorectal <sup>2</sup> – Peutz-Jeghers syndrome
<i>TP53</i>	<u>Increased Risk of Breast Cancer</u> See NCCN guidelines for Li-Fraumeni Syndrome Management <sup>1</sup>	No increased risk of ovarian cancer

For patients with known familial pathogenic/likely pathogenic variant(s), NCCN recommends testing for the specific familial pathogenic/likely pathogenic variant(s).<sup>1</sup>

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The American College of Obstetricians and Gynecologists (ACOG)

In 2018, the ACOG issued a practice bulletin with recommendations for the management of hereditary breast and ovarian cancer syndrome.<sup>6</sup> The following recommendation were made on the basis of “good and consistent scientific evidence”:

- Genetic counseling is recommended for all women with ovarian epithelial cancer (this includes fallopian tube cancer or primary peritoneal cancer) and for individuals who have a personal or family history of breast cancer or ovarian cancer.
- Women with *BRCA* mutations or who carry another actionable deleterious mutation that is predisposing to breast cancer should be offered risk-reducing bilateral mastectomy.
- Women with *BRCA* mutations or who carry another actionable deleterious mutation predisposing to ovarian cancer should be offered risk-reducing bilateral salpingo-oophorectomy. The timing of risk-reducing bilateral salpingo-oophorectomy can be individualized based on the particular genetic mutation, the patient’s desires for future childbearing, and family history. Typically, risk-reducing salpingo-oophorectomy is recommended at age 35–40 years for *BRCA1* carriers with the highest lifetime risk of ovarian cancer, whereas women with *BRCA2* may consider delaying until age 40–45 years because of later onset of ovarian cancer.
- For a risk-reducing bilateral salpingo-oophorectomy, all tissue from the ovaries and fallopian tubes should be removed. Thorough visualization of the peritoneal surfaces with pelvic washings should be performed. Complete, serial sectioning of the ovaries and fallopian tubes is necessary, with microscopic examination for occult cancer.

In 2017, the ACOG issued a position statement opposing requirements that genetic counseling be provided solely by a “certified” genetic counselor before genetic testing is ordered.<sup>7</sup> Authors affirmed that obstetrician-gynecologists are fully trained and qualified to counsel patients regarding genetic issues, and argued that such restrictions would impose unnecessary barriers to care.

**POLICY SUMMARY**

Evidence is sufficient to support the use of genetic testing for hereditary breast and ovarian cancer among patients with a known breast and/or ovarian cancer mutation, and patients with and without a personal history of cancer. Studies continue to indicate that genetic testing of these populations can lead to a change in patient management, informing clinical management strategies (e.g., surveillance strategies, prophylactic measures) that would otherwise have been missed by testing only 1 or 2 genes (e.g., *BRCA1/2*). Testing also conferred eligibility for prophylactic procedures, and was informative for family members who subsequently became eligible for genetic counseling/testing, increased disease surveillance, and/or prophylactic procedures. In addition, recent evidence-based clinical practice



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guidelines from the National Comprehensive Cancer Network and the American College of Obstetricians and Gynecology continue to support genetic testing for appropriate patients.

Evidence does not support genetic panel testing which include additional genes not identified as hereditary breast and/or ovarian cancer gene mutation(s) as a method of cancer risk assessment. Additional studies assessing analytical and clinical validity and clinical utility to demonstrate these tests' benefit are needed.

## **INSTRUCTIONS FOR USE**

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days' notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

## **REGULATORY STATUS**

### Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

## **MEDICAL POLICY CROSS REFERENCES**

- Genetic Testing: Pharmacogenetic Testing (All Lines of Business except Medicare)
- Genetic Testing: Non-Covered Genetic Panel Tests (All Lines of Business except Medicare)

## **REFERENCES**

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7. American College of Obstetricians and Gynecologists (ACOG). Access to Genetic Testing: Position Statement. <https://www.acog.org/Clinical-Guidance-and-Publications/Position-Statements/Access-to-Genetic-Testing?IsMobileSet=false>. Published 2018. Accessed 3/24/2021.