GENETIC TESTING FOR HEREDITARY CANCER

Policy Number: 2018T0009W

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INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Medical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Medical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE RATIONALE

Genetic counseling is strongly recommended prior to these tests in order to inform persons being tested about the advantages and limitations of the test as applied to a unique person.

Hereditary Breast and Ovarian Cancer (BRCA1/BRCA2)

Genetic testing for BRCA1 and BRCA2 for individuals with a personal history of a related cancer is proven and medically necessary in the following situations:
- Women with a personal history of breast cancer in the following situations:
  - Breast cancer diagnosed at any age in an individual with at least one close (1st-, 2nd-, and 3rd-degree relative) blood relative who has a BRCA1 or BRCA2 mutation (testing should be targeted to the known BRCA1/BRCA2 mutation in the family. Further BRCA1/BRCA2 testing should only be pursued if the results are negative and the patient otherwise meets testing criteria)
  - Breast cancer diagnosed at any age in an individual from one of the following ethnic groups associated with founder mutations:
    - Ashkenazi Jewish (Testing for Ashkenazi Jewish founder-specific mutations should be performed first. Further BRCA1/BRCA2 testing should only be pursued if the results are negative and the patient otherwise meets testing criteria without considering Ashkenazi Jewish ancestry.)
  - Breast cancer diagnosed at age 45 or younger or “triple-negative” (Her2 negative, ER negative and PR negative) breast cancer diagnosed at age 60 or younger; or breast cancer diagnosed at age 50 or younger with:
    - Bilateral breast cancer; or
    - A personal history of a prior primary breast cancer diagnosis; or
    - At least one close blood relative with breast cancer; or
    - At least one close blood relative with pancreatic cancer; or
    - At least one close blood relative with prostate cancer; or
    - An unknown or limited family history (see Definitions section for further clarification of limited family history).
  - Breast cancer diagnosed at any age with:
    - At least one close male blood relative with breast cancer diagnosed at any age; or
    - At least one close blood relative with breast cancer diagnosed at age 50 or younger; or
    - At least two close blood relatives on the same side of the family with breast cancer at any age; or
    - At least one close blood relative with ovarian cancer at any age; or
    - At least two close blood relatives on the same side of the family with pancreatic and/or prostate cancer at any age.
  - Metastatic breast cancer and may be a candidate for treatment with a PARP inhibitor (e.g., olaparib).
- Men with a personal history of breast cancer.
- Women with a personal history of ovarian cancer.
- Women and men with a personal history of pancreatic cancer at any age and at least one close blood relative with:
  - Ovarian cancer at any age, or
  - Breast cancer diagnosed with at age 50 or younger, or
  - Two relatives on the same side of the family with breast, pancreatic and/or prostate cancer at any age.
- Women and men with a personal history of pancreatic cancer and Ashkenazi Jewish ancestry. Testing should be targeted to the known Ashkenazi Jewish founder-specific mutations.
- Men with a personal history of high risk prostate cancer (Gleason score ≥7) at any age and
  - At least one close blood relative with ovarian cancer at any age or breast cancer (≤ age 50 years); or
  - At least two close relatives on the same side of the family with breast, pancreatic and/or prostate cancer at any age.

**Genetic testing for BRCA1 and BRCA2 for individuals without a personal history of a related cancer is proven and medically necessary in the following situations:**
- When there is a known BRCA1/BRCA2 mutation in a close blood relative (defined as first-, second- or third-degree relative). Testing should be targeted to the known BRCA1/BRCA2 mutation in the family. Further BRCA1/BRCA2 testing should only be pursued if the results are negative and the patient otherwise meets other testing criteria.
- When there is at least one of the following familial risk factors:
  - At least one first- or second-degree blood relative meeting any of the above criteria for individuals with a personal history of a related cancer; or
  - At least one third-degree blood relative with breast cancer and/or ovarian cancer who has at least 2 close blood relatives with breast cancer (at least one with breast cancer at age 50 or younger) and/or ovarian cancer.

**Genetic testing for BRCA1 and/or BRCA2 testing is unproven and not medically necessary for all other indications including:**
- Screening for breast or ovarian cancer risk for individuals not listed in the proven indications above; or
- For risk assessment of other cancers. Further evidence is needed to establish the clinical utility of testing in other populations.

**Multi-Gene Hereditary Cancer Panel Testing Criteria**
Genetic testing with a multi-gene hereditary cancer panel in individuals with an indication for testing for hereditary breast and ovarian cancer is proven and medically necessary if all of the following criteria are met:
• The patient meets at least one of the criteria in Hereditary Breast and Ovarian Cancer (BRCA1/BRCA2) (see above section); and
• The patient has a family history or personal history that is strongly suggestive of more than one hereditary cancer syndrome; and
• The suspected hereditary cancer syndromes can be diagnosed by testing of one or more genes included in the specific hereditary cancer panel; and
• The results of testing will directly impact this patient’s medical management.

Genetic testing with a multi-gene cancer panel in individuals with an indication for testing for hereditary colorectal cancer is proven and medically necessary in the following situations:
• The patient meets at least one of the following criteria for a hereditary colorectal cancer (Lynch) syndrome:
  o Men with a personal history of colorectal cancer or women with a personal history of colorectal or endometrial cancer diagnosed at age 49 or younger; or
  o Men with a personal history of colorectal cancer or women with a personal history of colorectal or endometrial cancer diagnosed at age 50 or later with at least one of the following criteria:
    ▪ A personal history of another cancer associated with Lynch Syndrome; or
    ▪ At least one first-degree relative with colorectal or endometrial cancer diagnosed at age 49 or younger; or
    ▪ At least two close relatives with a cancer associated with Lynch Syndrome; or
    ▪ Tumor testing results showing that their colorectal or endometrial cancer was MSI-high or had immunohistochemical (IHC) staining showing the absence of one or more mismatch repair proteins (MLH1, MSH2, MSH6 or PMS2); or
    ▪ PREMM 1,2,6 score of 5% or greater
  o A personal history of colorectal polyposis with at least 10 adenomatous polyps; or
  o At least one close blood relative meeting the criteria for Lynch Syndrome (as defined in the first two criteria above) or with a clinical diagnosis of familial adenomatous polyposis in whom genetic testing was not or cannot be completed; or
  o PREMM5 score of 2.5% or greater or PREMM1,2,6 score of 5% or greater for having a Lynch syndrome gene mutation
  and
• The suspected hereditary cancer syndromes can be diagnosed by testing of one or more genes included in the specific hereditary cancer panel; and
• The results of testing will directly impact this patient’s medical management.

Genetic testing with a multi-gene hereditary cancer panel in individuals without an indication for testing for hereditary breast and ovarian cancer or colorectal cancer is proven and medically necessary in the following situations:
• The patient has a family history or personal history that is strongly suggestive of more than one hereditary cancer syndrome; and
• The suspected hereditary cancer syndromes can be diagnosed by testing of one or more genes included in the specific hereditary cancer panel; and
• The results of testing will directly impact this patient’s medical management.

Genetic testing with a multi-gene cancer panel is proven and medically necessary in a patient has previously tested negative (indeterminate) for the high penetrance genes that are most likely to explain the personal or family history of cancer (e.g., BRCA1/2 for breast cancer and ovarian cancer) in the following situations:
• The patient’s personal and family history remains strongly suggestive of an inherited susceptibility that can be diagnosed by testing of one or more genes included in the specific hereditary cancer panel; and
• The results of testing will directly impact this patient’s medical management.

Multi-gene hereditary cancer panels are unproven and not medically necessary for all other indications.

**DEFINITIONS**

1st, 2nd, and 3rd Degree Relatives: Blood relatives on the same side of the family (maternal or paternal).
• 1st-degree relatives are parents, siblings, and children.
• 2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.
• 3rd-degree relatives are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.

PREMM: PREdiction Model for gene Mutations. The PREMM model estimates the overall cumulative probability of having an MLH1, MSH2, MSH6, PMS2, and EPCAM gene mutation.
The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

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<th>CPT Code</th>
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<tr>
<td>81162</td>
<td>BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis</td>
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<td>81211</td>
<td>BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (i.e., exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)</td>
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<td>81212</td>
<td>BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants</td>
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<td>BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; uncommon duplication/deletion variants</td>
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<td>BRCA1 (breast cancer 1) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants (i.e., exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)</td>
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<td>81215</td>
<td>BRCA1 (breast cancer 1) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant</td>
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<td>81216</td>
<td>BRCA2 (breast cancer 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis</td>
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<td>81217</td>
<td>BRCA2 (breast cancer 2) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant</td>
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<td>81432</td>
<td>Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53</td>
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<tr>
<td>81433</td>
<td>Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11</td>
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**DESCRIPTION OF SERVICES**

The National Comprehensive Cancer Network (NCCN) guidelines on genetic/familial high-risk assessment for breast and ovarian cancer state that significant limitations of interpreting test results for an individual without a cancer diagnosis should be discussed. If there are no living family members with breast or ovarian cancer available for testing, consider testing family members affected with other cancers associated with BRCA1/BRCA2, such as prostate cancer (Gleason score ≥7), pancreatic cancer or melanoma. Testing of individuals without a cancer diagnosis should only be considered when there is no affected family member available for testing (NCCN, 2016).

Genetic testing for hereditary cancer susceptibility is used to predict an individual's risk of cancer development in the future. It has been estimated that 5-10% of all cancers are hereditary (the result of inherited genetic susceptibility).

**Hereditary Breast and Ovarian Cancer (BRCA1/BRCA2)**

Breast cancer is the second most common cause of cancer-related deaths among women. The inherited tendency to develop breast and ovarian cancer has been termed the hereditary breast and ovarian cancer syndrome (HBOC). Mutation in either of two genes, BRCA1 and BRCA2, has been associated with an increased risk for breast cancer and ovarian cancer. A deleterious mutation in either gene may be inherited from either parent; and later an acquired mutation of the other allele can lead to cancer development.

It has been estimated that inherited BRCA1 and BRCA2 mutations account for 5 to 10 percent of breast cancers and 10 to 15 percent of ovarian cancers among white women in the United States (National Cancer Institute [NCI], 2015).
Harmful BRCA1 mutation may also increase a woman’s risk of developing other cancers. Men with a harmful BRCA1 mutation also have an increased risk of breast cancer and, possibly, of pancreatic cancer, testicular cancer, and early-onset prostate cancer. However, male breast cancer, pancreatic cancer, and prostate cancer appear to be more strongly associated with BRCA2 gene mutation (Thompson and Eaton, 2002; NCCN, 2017).

**Multi-Gene Hereditary Cancer Panels**

Multi-gene hereditary cancer panels using next generation sequencing technology are currently available, and many different test panels are marketed commercially, most of which also include large deletion/duplication analysis. These panels are intuitively attractive because they can rapidly test for numerous mutations both within a single gene and across multiple genes related to increased cancer risks. It is also possible that these multi-gene tests can, in the case of families where more than one hereditary cancer syndrome is suspected, be performed more cost effectively than stepwise individual gene testing. However, many of these panel tests also include low to moderate-risk genes that may result in the identification of gene mutations that are of unclear clinical significance or which would not clearly direct a patient’s medical management recommendations. Identification of mutations for which the clinical management is uncertain may lead to unnecessary follow-up testing and procedures, all of which have their own inherent risks (NCCN, 2016; LaDuca et al., 2014; Robson et al., 2015; Kurian et al., 2014; Tung et al., 2015; Plon et al., 2011).

**CLINICAL EVIDENCE**

**Hereditary Breast and Ovarian Cancer (BRCA1/BRCA2)**

National Comprehensive Cancer Network (NCCN) guidelines present specific criteria for genetic testing for hereditary breast and/or ovarian cancer syndrome. The guidelines address genetic risk assessment, counseling, testing and management based on test results (NCCN, 2016).

Several studies have shown that BRCA1 breast cancer is more likely to be characterized as triple-negative. Studies have reported BRCA1 mutations in 9-28% of patients with triple-negative breast cancer. In addition, it appears that among patients with triple-negative disease, BRCA mutation carriers were diagnosed at a younger age compared with non-carriers (NCCN, 2016).

In a Cochrane systematic review, Hilgart et al. (2012) evaluated the impact of cancer genetic risk-assessment services on patients at risk of familial breast cancer. In this update, the authors included five new trials, bringing the total number of included studies to eight. The included trials provided data on 1973 participants and assessed the impact of cancer genetic risk assessment on outcomes including perceived risk of inherited cancer, and psychological distress. The review suggests that cancer genetic risk-assessment services help to reduce distress, improve the accuracy of the perceived risk of breast cancer and increase knowledge about breast cancer and genetics. The review found favorable outcomes for patients after risk assessment for familial breast cancer.

**Professional Societies**

**American College of Obstetricians and Gynecologists (ACOG)**

In a 2009 practice bulletin (reaffirmed 2015), the ACOG recommended criteria for genetic risk assessment of hereditary breast and ovarian cancer syndrome (HBOC). These recommendations conclude:

- BRCA positive women should be offered salpingo-oophorectomy by age 40 or when childbearing is completed.
- 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.
- Genetic risk assessment is recommended for patients with a greater than an approximate 20-25% chance of having an inherited predisposition to breast cancer and ovarian cancer. This includes women with the following:
  - A close relative (mother, sister, daughter, grandmother, granddaughter, aunt or niece) with a known BRCA mutation
  - Personal history of both breast and ovarian cancer
  - Ovarian cancer and a close relative with ovarian cancer or premenopausal breast cancer or both
  - Ovarian cancer and Ashkenazi Jewish ancestry
  - Breast cancer by age 40 years and Ashkenazi Jewish ancestry
  - Breast cancer by age 50 years and a close relative with ovarian cancer or male breast cancer

**American Society of Clinical Oncology (ASCO)**

An ASCO policy statement recommends that genetic testing for cancer susceptibility be performed when the following three criteria are met: the individual being tested has a personal or family history suggestive of genetic cancer susceptibility; the test can be adequately interpreted; and the test results have accepted clinical utility (Robson et al., 2015).
National Society of Genetic Counselors (NSGC)

The NSGC recommends that genetic testing be performed in the context of an informed decision-making process (Berliner et al., 2013). The process of cancer risk assessment and genetic counseling for hereditary breast and ovarian cancer syndrome requires many steps, including the following:

- Gathering personal medical and family history data
- Psychosocial assessment
- Discussion of cancer and mutation risk and how personalized risk estimates are derived
- Facilitation of the informed consent process through discussion of the risks, benefits, limitations, and likelihood of identifying a mutation with genetic susceptibility testing
- Results disclosure (if applicable)
- Discussion of medical management options
- Review of issues related to genetic discrimination

U.S. FOOD AND DRUG ADMINISTRATION (FDA)


CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) specifically addressing genetic testing for hereditary cancer. Local Coverage Determinations (LCDs) exist; refer to the following LCDs at https://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?kq=true:

- BRCA1 and BRCA2 Genetic Testing
- MolDX: BRCA1 and BRCA2 Genetic Testing
- MolDX: Molecular Diagnostic Tests (MDT)
- Molecular Diagnostic Tests (MDT)
- Molecular Pathology Procedures
- Pathology and Laboratory: BRCA1 and BRCA2 Genetic Testing

(Accessed June 29, 2017)

REFERENCES


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<td>01/01/2018</td>
<td>• Updated list of applicable CPT codes to reflect annual code edits; revised</td>
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