



INLAND EMPIRE HEALTH PLAN

IEHP UM Subcommittee Approved Authorization Guidelines
Genetic Testing for BRCA1 and BRCA2 Mutations for Assessing BRCA Related Cancer Risk

Policy:

Based on our review of Medical, NCCN, USPSTF, ACOG, ASBS, and other provider guidelines, the IEHP UM Subcommittee adopted the following recommendations for harmful *BRCA1* and *BRCA2* gene mutation testing as a covered benefit for adults who meet the criteria below. This is a once a lifetime procedure. IEHP also recommends genetic counseling prior to BRCA testing.

Individuals who should be tested for harmful *BRCA1* or *BRCA2* mutations:

A) Personal history of breast cancer and one or more of the following:

- Diagnosed at 45 years or younger; OR
- Diagnosed between 46 and 50 years with one of the following:
 - An additional primary breast cancer; OR
 - One or more first-, second-, or third-degree blood relative(s) on the same side of the family diagnosed with breast cancer at any age; OR
 - An unknown family history or a limited family history where fewer than two first- or second-degree female relatives lived beyond age 45 in either family lineage; OR
- Diagnosed at 60 years or younger with a triple negative breast cancer; OR
- Diagnosed at any age with one of the following:
 - One or more first-, second-, or third-degree blood relative(s) on the same side of the family with breast cancer diagnosed at 50 years or younger; OR
 - Two or more first-, second-, or third-degree blood relatives on the same side of the family diagnosed with breast cancer at any age; OR
 - One or more first-, second-, or third-degree blood relative(s) on the same side of the family diagnosed at any age with ovarian, fallopian tube, or primary peritoneal cancer; OR
 - Two or more first-, second-, or third-degree blood relatives on the same side of the family diagnosed with pancreatic cancer at any age and/or prostate cancer (Gleason score of 7 or higher); OR

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- A first-, second-, or third-degree male blood relative diagnosed at any age with breast cancer; OR
- An ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish, Icelandic, Swedish, or Hungarian). No additional family history may be required.

B) Women without breast cancer who have a family history of any of the following:

- A first- or second-degree blood relative meeting any of the criteria above (Section A); OR
- A third-degree blood relative with breast, ovarian, fallopian tube, or primary peritoneal cancer with one of the following:
 - Two or more first-, second-, or third-degree blood relatives on the same side of the family diagnosed with breast cancer with at least one diagnosed at 50 years or younger; OR
 - Two or more first-, second-, or third-degree blood relatives on the same side of the family diagnosed at any age with ovarian, fallopian tube, or primary peritoneal cancer.

C) Women diagnosed at any age with ovarian, fallopian tube, or primary peritoneal cancers.

D) Person with a close blood relative with a known *BRCA1* and/or *BRCA2* genetic mutation.

E) Men with breast cancer at any age.

F) Personal history of pancreatic cancer or prostate cancer (Gleason score of 7 or higher) diagnosed at any age with two or more first-, second-, or third-degree blood relatives on the same side of the family diagnosed at any age with breast, ovarian, fallopian tube, primary peritoneal, pancreatic, and/or prostate cancer (Gleason score of 7 or higher).

- For pancreatic cancer, if Ashkenazi Jewish ancestry, only one additional affected relative is needed.

G) Person who does not meet any of the above criteria above but upon evaluation by a genetic specialist is recommended to have *BRCA1* or *BRCA2* mutation testing.

Testing for *BRCA1* or *BRCA2* mutations is inappropriate in the following individuals:

A) Children who are 17 years old or younger.

- The chances of a child developing a *BRCA*-related cancer are very low even if there is a known *BRCA* mutation in the family.
- There is no known risk-reduction strategy for children.
- If there is a known *BRCA* mutation in close blood relatives, these children may want to pursue further testing after becoming adults at 18 years of age.

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B) Individuals with unknown family history who do not have an early onset *BRCA*-related cancer or male breast cancer.

C) Individuals without a family history associated with an increased risk of *BRCA1* or *BRCA2* gene mutations.

D) *BRCA* testing is not recommended for surveillance testing in men or for screening of any cancers (ex. breast, ovarian, prostate, or pancreatic) as its effectiveness has not been established.

Rationale:

Medi-cal ⁸:

BRCA1 and *BRCA2* gene sequence analysis for susceptibility to breast and ovarian cancer.

- Women without diagnosis of breast and ovarian cancer
 - 2 first degree relatives with breast cancer, one of whom was diagnosed at ≤ 50 years; OR
 - A combination of three or more first- or second-degree relatives with breast cancer regardless of age at diagnosis; OR
 - A combination of both breast and ovarian cancer among first- and second-degree relatives; OR
 - A first-degree relative with bilateral breast cancer; OR
 - A combination of two or more first- or second-degree relatives with ovarian cancer, regardless of age of diagnosis; OR
 - A first- or second- degree relative with both breast and ovarian cancer at any age; OR
 - History of breast cancer in a male relative; OR
 - For women of Ashkenazi Jewish decent, any first-degree relative (or two second-degree relatives on the same side of the family) with breast or ovarian cancer; OR
- A family history of breast or ovarian cancer that includes a relative with a known deleterious *BRCA* mutation; OR
- A personal history of breast cancer plus one or more of the following:
 - Diagnosed at ≤ 45 ; OR
 - Diagnosed at age ≤ 50 with ≥ 1 close blood relative(s) with breast cancer diagnosed at ≤ 50 and/or ≥ 1 close blood relative(s) with epithelial ovarian cancer at any age; OR
 - Two breast primaries when first breast cancer diagnosis occurred at age ≤ 50 ; OR
 - Diagnosed at age ≤ 60 with a triple negative breast cancer; OR
 - Diagnosed at age ≤ 50 with a limited family history; OR
 - Diagnosed at any age, with ≥ 2 close blood relatives with pancreatic cancer at any age; OR
 - Close male blood relative with breast cancer; OR
 - For an individual of ethnicity associated with higher mutation frequency (for example, founder populations of Ashkenazi Jewish, Icelandic, Swedish, Hungarian, or other) no additional family history may be required; OR
- Personal history of epithelial ovarian cancer/fallopian tube/primary peritoneal cancer; OR

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- Personal history of male breast cancer; OR
- Personal history of pancreatic cancer at any age with ≥ 2 close blood relatives with breast and/or ovarian and/or pancreatic cancer at any age.

NCCN Guidelines³:

BRCA1 and *BRCA2* harmful genetic mutation testing should be done in individuals at high risk of hereditary breast and/or ovarian cancer syndrome as indicated below^{a,b,c}:

- Individual from a family with a known deleterious *BRCA1/BRCA2* mutation
- Personal history of breast cancer^b + one or more of the following:
 - Diagnosed age ≤ 45 y
 - Diagnosed age ≤ 50 y with:
 - An additional primary^d
 - ≥ 1 close blood relative^e with breast cancer at any age
 - Unknown or limited family history^a
 - Diagnosed ≤ 60 y with a:
 - Triple negative breast cancer
 - Diagnosed at any age with:
 - ≥ 1 close blood relative^e with breast cancer diagnosed at ≤ 50 y
 - ≥ 2 close blood relatives^e with breast cancer at any age
 - ≥ 1 close blood relative^e with epithelial ovarian^f cancer
 - ≥ 2 close blood relatives^e with pancreatic cancer and/or prostate cancer (Gleason score ≥ 7) at any age
 - A close male blood relative^e with breast cancer
 - For an individual of ethnicity associated with higher mutation frequency (e.g./ Ashkenazi Jewish), no additional family history may be required^g
- Personal history of epithelial ovarian^f cancer
- Personal history of male breast cancer
- Personal history of pancreatic cancer or prostate cancer (Gleason score ≥ 7) at any age with ≥ 2 close blood relatives^e with breast and/or ovarian^f and/or pancreatic or prostate cancer (Gleason score ≥ 7) at any age
 - For pancreatic cancer, if Ashkenazi Jewish ancestry, only one additional affected relative is needed.

Key:

- a. Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management. The probability of mutation detection associated with these criteria will vary based on family structure. Individuals with unknown or limited family history/structure such as fewer than 2 first- or second-degree female relatives having lived beyond age 45 in either lineage, may have an underestimated probability of familial mutation detection. The likelihood of mutation detection may be very low in families with a large number of unaffected female relatives. Clinical judgment should be used to determine the appropriateness of genetic testing. The maternal and paternal sides should be considered independently.
- b. For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.

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- c. Patients who have received an allogeneic bone marrow transplant should not have molecular genetic testing via blood or buccal samples due to the unreliable test results from contamination by donor DNA. 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.
- d. Two breast primaries, includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either synchronously or asynchronously.
- e. Close blood relatives include first-, second-, and third-degree relatives on the same side of the family.
- f. For the purposes of these guidelines, fallopian tube and primary peritoneal cancers are included. Ovarian/fallopian tube/primary peritoneal cancers are component tumors of Lynch syndrome/hereditary non-polyposis colorectal cancer; be attentive for clinical evidence of this syndrome.
- g. Testing for Ashkenazi Jewish founder-specific mutations should be performed first. Full sequencing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or if other HBOC criteria are met. Founder mutations exist in other populations.

USPSTF Recommendations ⁶:

Screen women whose family history may be associated with harmful *BRCA* mutations:

If screening is positive, patients should be referred to genetic counselor, and if indicated after counseling, *BRCA* testing.

- Positive result on screening tool:
 - Ontario Family History Assessment Tool
 - Referral with score ≥ 19
 - Manchester Scoring System
 - Referral with score of ≥ 10 in either column or ≥ 15 for both columns
 - Referral Screening Tool
 - Referral if ≥ 2 items checked
 - Pedigree Assessment Tool
 - Referral if score ≥ 8
 - Family History Screen 7
 - Referral if ≥ 1 positive response
- Family member with breast cancer diagnosis before 50 years old
- Bilateral breast cancer
- Family history of ovarian cancer
- Presence of breast cancer in one or more male relatives
- Family history of multiple individuals with breast cancer
- A family member with 2 primary types of *BRCA* related cancer (breast, ovary, fallopian, etc)
- Ashkenazi Jewish ethnicity

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American Society for Breast Surgeons ²:

The society agrees with the NCCN 2010 guidelines, USPSTF guidelines 2013, and Medical's standards with the following variations:

- *BRCA* testing should be done in persons with early onset breast cancer before age 50, instead of age 45.

AETNA ⁹:

This company agrees with the NCCN 2010 guidelines, USPSTF guidelines 2013, and Medical's standard with the following variations:

- Women who do not meet any of the above criteria but are determined through both independent formal genetic counseling and validated quantitative risk assessment tool⁷ to have at least a 10% pre-test probability of carrying a *BRCA1* or *BRCA2* mutation.
 - Note: A 3-generation pedigree and quantitative risk assessment result must be provided to Aetna.

Anthem ¹⁰:

This company agrees with the NCCN 2010 guidelines, USPSTF guidelines 2013, and Medical's standard with the following variations:

- For individuals with a family history of cancer:
 - The individual for whom the test is requested, has a first- or second-degree relative who had triple negative breast cancer diagnosed at age 60 or less; OR
 - The individual has a first- or second-degree relative who has a history of ovarian cancer and 2 or more first-, second-, or third-degree relatives on the same side of the family with pancreatic cancer; OR

CIGNA ¹¹:

This company agrees with the NCCN 2010 guidelines, USPSTF guidelines 2013, and Medical's standard with the following variations:

- Coverage is provided if there is a Family History of Breast, Ovarian or Pancreatic Cancer:
 - First or second degree relative who is diagnosed at any age with breast cancer with two or more relatives with pancreatic cancer or prostate cancer (Gleason score ≥ 7); OR

Background:

***BRCA1* and *BRCA2* Related Cancers:**

BRCA1 and *BRCA2* are genes in the DNA code of all humans. They tell the body how to make proteins which are needed to help stop cancers from forming. When the *BRCA1* or the *BRCA2* gene sequences are damaged or mutated the body can no longer form these proteins and some of the protection against cancer is lost.

Though, *BRCA* mutations are rare (1 in 300-500 people), *BRCA* related cancers are usually more aggressive and occur at younger ages. Men have a higher risk of developing breast or prostate

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cancer. Both have a slightly increased risk of pancreatic cancer. Women become more likely to get breast, ovarian, or other cancers of the reproductive system. In the general population, one in eight women will develop breast cancer during her lifetime, but when a harmful *BRCA1* or *BRCA2* mutation is present, almost half of these women will develop breast cancer before 70 years of age.^{6,7}

Genetic testing is recommended for women who have a family or personal history suggestive of a *BRCA* gene mutation, have access to accurate result interpretation, and the results will be helpful in the patient’s future medical care.⁶ Men should consider getting genetic testing if they have breast cancer, pancreatic cancer, or prostate cancer with a family history consistent with *BRCA* related cancers.

Some ethnicities have higher rates of *BRCA1* or the *BRCA2* gene mutations. These mutations are prevalent in 2.1% of Ashkenazi Jewish women. Globally, Norwegian, Dutch, and Icelandic populations also have a higher prevalence of harmful *BRCA* gene mutations. Women from these ethnicities who have a personal or family history of breast cancer are at higher risk of having a *BRCA* mutation and may be candidates for genetic testing.^{3,6,7}

All individuals should be offered genetic counseling by trained professionals before laboratory testing is done as this has been shown to decrease testing in people who are unlikely carriers, and decrease cancer related worry, anxiety and depression.^{6,7}

Treatment Options:

Treatment options for those who test positive to *BRCA 1* or the *BRCA 2* are available and include more frequent screening for cancer, risk-reducing surgeries (bilateral mastectomy or salpingo-oophorectomy), or risk-reducing medications (oral contraceptives, vitamins, tamoxifen or raloxifene).¹

Risks of Genetic Testing:

Direct medical risks from the medical testing are very minimal. Patients may experience some worry, anxiety, or sleep problems about possible cancer after being tested and found to be positive for the *BRCA* genetic mutations. Others may feel survivor guilt or more carefully consider marriage and childbearing, as the mutation has a 50% chance of being passed on.¹

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