BRCA 1/2
Breast cancer testing
THINK ABOUT TOMORROW, TODAY
5–10% of patients with breast and/or ovarian cancer have a hereditary form\(^1\). For any individual carrying a mutation in BRCA1 or BRCA2, the lifetime risk of developing breast/ovarian cancer increases from 12% to 50–85\(^2\).
BRCA1/2 are a key factor in breast and ovarian cancer development

Breast and ovarian cancers are common, they are the first and fifth most common cancers that occur in women\(^2\). Hereditary forms of breast and ovarian cancer account for 5-10\% of all cases diagnosed, and an association with mutations in the BRCA1/2 genes has been clearly demonstrated\(^1\).

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BRCA1/2 increase the lifetime risk of developing cancer

In the general population, approximately 12% of women will develop breast cancer in their lifetime. In comparison, 55-65% of women carrying a BRCA1 mutation and ~45% of women carrying a BRCA2 mutation will develop breast cancer by age 70.
By detecting cancer early, patients can have timely access to preventative measures and proactive treatment – leading to a better prognosis overall.

Where cancer has been diagnosed, somatic testing of the BRCA1/2 genes is still highly beneficial and can significantly improve the prognosis and quality of life of cancer-affected patients. Somatic mutation analysis of tumors can identify therapeutic sensitizing and resistance mutations. This allows a more detailed assessment of the diagnosis, prognosis and can help identify targeted therapies directed towards the individual patient’s tumor profile. For example, new drugs that specifically target the BRCA1/2 signaling pathways have been approved.

Our team of hereditary and somatic cancer experts can support you at every step of your patient’s journey.

**BRCA1/2 testing at CENTOGENE**

DNA is analyzed from a patient blood or tissue sample. CENTOGENE can perform genetic testing from dried blood spots collected on easy-to-use filter cards. You have the choice of requesting full sequencing of BRCA1 and BRCA2, allowing comprehensive analysis and consideration of every variant detected across both genes. In addition, CENTOGENE offers testing specifically for duplication or deletion of either gene either as a standalone test or in conjunction with the full sequencing service.
When to perform BRCA1/2 testing

BRCA1 and BRCA2 testing is especially recommended when a patient’s personal or family history shows any of the following:

- Breast cancer diagnosed at 50 or younger*
- Ovarian cancer at any age
- Multiple breast cancers, bilateral or ipsilateral*
- Breast and ovarian cancer
- Male breast cancer*
- Triple-negative (estrogen receptor negative, progesterone receptor negative and HER2/neu negative) breast cancer
- Pancreatic cancer with breast or ovarian cancer in the same individual, or on the same side of the family
- Two or more relatives with breast cancer, one under age 50
- Three or more relatives with breast cancer at any age
- A previously identified BRCA1 or BRCA2 mutation in the family*

CENTOGENE recommends that all genetic testing is conducted together with pre and post-test counseling by a qualified genetic counselor. For unaffected persons with a strong family history, analysis of an affected family member is recommended.

* According to the Evidence-Based Cancer Guidelines, National Comprehensive Cancer Network (NCCN)
What are the possible outcomes of the test?

A) POSITIVE

If the test identifies a disease mutation, then only a predisposition to breast and/or ovarian cancer is confirmed. This does not necessarily mean that the patient has cancer or will develop it. However, depending on the mutation, the patient will have an increased likelihood of developing cancer 46-87% over the lifetime.

B) NEGATIVE

If the genetic test does not identify a predisposing BRCA1/2 mutation, then the patient’s individual risk of developing breast/ovarian cancer is low (the risk of developing breast cancer in the general population is 12%). A negative test result should be discussed to see what individual cancer screening prevention programs might be appropriate for the patient.

C) INCONCLUSIVE

Not all mutations in BRCA1/2 are disease causing. Many disease-causing mutations have been confirmed but not all. In some instances, the test may identify a mutation in BRCA1/2 which cannot be conclusively characterized as disease causing. In such cases, CENTOGENE will send an update if the classification of the mutation changes the clinical consequence in future.
WHEN A PATHOGENIC BRCA1/2 MUTATION IS DETECTED

Patients with a significantly increased breast cancer risk due to an inherited variant should be informed about possibilities of individual risk reduction. If a BRCA1/2 mutation is identified, regular screening, prophylactic treatment or surgery are all options that should be discussed with a genetic counsellor and the treating clinician.

Where an inherited mutation in BRCA1/2 is identified in a family, testing of at-risk relatives can identify those family members who also carry the mutation, and may benefit from preventive action. Germline mutations in BRCA1/2 are inherited in an autosomal dominant manner. This means any offspring of an individual with a BRCA1/2 mutation has a 50% chance of inheriting the mutation, and should be offered genetic analysis for the identified variant.

WHEN NO CLEAR PATHOGENIC BRCA1/2 MUTATION IS DETECTED

If no mutation in BRCA1 or BRCA2 is identified, the following explanations must be considered:

› The case is not due to an inherited BRCA1/2 variant, but is a sporadic case (risk of breast cancer is 12%)
› The causative mutation is in an intron, or in a regulatory element that cannot be identified with routine diagnostic methods
› Other disorders with elevated risk of breast and/or ovarian carcinoma should be considered (Li-Fraumeni syndrome, Cowden syndrome, hereditary diffuse gastric cancer, Peutz-Jeghers-type hamartomatous polyps)

For patients who are BRCA1/BRCA2 negative, we offer alternative gene panels including additional genes linked to hereditary breast and/or ovarian cancer.
**High risk of hereditary breast cancer**

**BACKGROUND**

Your patient has one 1st degree relative with ovarian cancer (diagnosed before age 50) and one 2nd degree relative with bilateral breast cancer (diagnosed before age 50).
Accordingly USPSTF, BRCA1 and BRCA2 testing is not suggested for healthy women in the absence of family history of cancer\textsuperscript{3,4}.

As family pedigrees are not always informative due to smaller families or unavailable information, BRCA1/2 screening might also be offered in these cases to identify high risk individuals and to offer them the same diagnostic and therapeutic options.

CENTOGENE offers BRCA1/2 breast cancer testing, to identify potentially harmful mutations in BRCA1/2 genes that could be associated with increased risk for cancer in family members. The test can be performed in 15 days, from a minimal amount of sample (2µg DNA, 2ml EDTA blood or 1 filtercard). We sequence full BRCA1/BRCA2 genes with a 100% coverage at a minimum of 20x or greater, or perform hotspot testing depending on the patient clinical presentations and family history.

The probability to identify BRCA1/2 mutation is high (approx. 30%) due to the family history with mother and aunt diagnosed with breast/ovarian cancers at an early age.

- Identification of a pathogenic variant would confirm the significantly increased lifetime risk for breast and ovarian cancer
- Genetic counselling needs to be offered
- Individualized surveillance and potential therapy options must be discussed
- Genetic counselling and carrier analysis to siblings should be offered

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\textsuperscript{3.} Antoniou et al, 2003; Chen and Parmigiani, 2007#
\textsuperscript{4.} Moyer VA, 2014
BRCA1/2 testing at CENTOGENE

NGS PANEL PLUS

Turnaround Time: 15 days
Coverage: 100% of target region covered
Required Material: ≥ 2μg DNA or
≥ 1ml EDTA Blood or
≥ 1 filtercard

DELETION/DUPLICATION TESTING

Turnaround time: 15 days (if performed together with sequencing)
MLPA Analysis of: BRCA1, BRCA2
Required Material: ≥ 2μg DNA or
≥ 1ml EDTA Blood or
≥ 1 filtercard

SEQUENCING + DELETION/DUPLICATION PACKAGE

Turnaround Time: 15 days
Required Material: ≥ 4μg DNA or
≥ 1ml EDTA Blood or
≥ 1 filtercard

SOMATIC MUTATION ANALYSIS

Turnaround Time: 10 days
Coverage: Mean 1000x
Required Material: at least 10 FFPE section of thickness 5-10µm with marked area of enriched tumor and accompanying pathology report or ≥ 2μg DNA from tumor enriched section
Please visit our website for more information:

www.centogene.com

CONTACT DETAILS:

CENTOGENE AG
Am Strande 7
18055 Rostock
Germany

.customer.support@centogene.com
+49 (0)381 80 113 - 416
+49 (0)381 80 113 - 401