CENTOGENE
THE RARE DISEASE COMPANY

# *BRCA1/2*

## Think about tomorrow, today

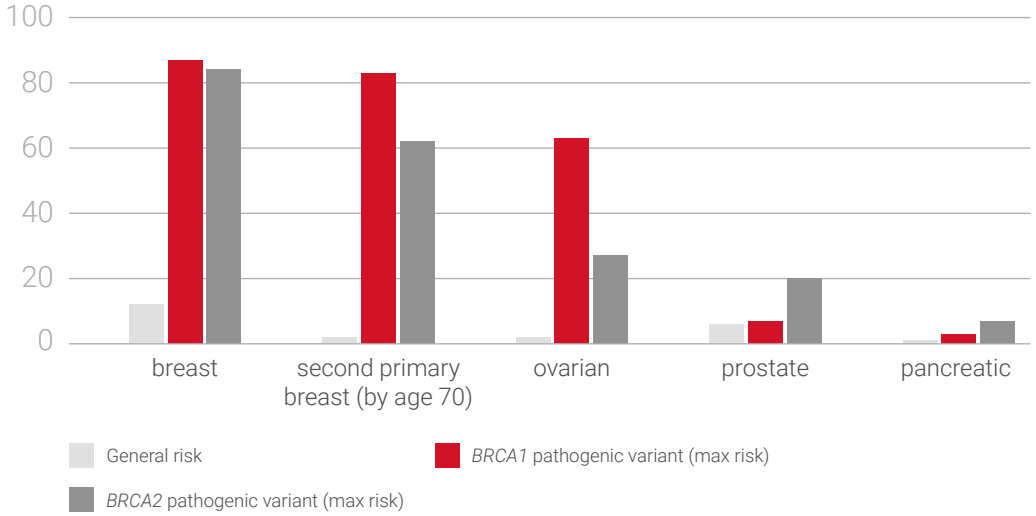
**BREAST CANCER TESTING**

Working together ...

# *BRCA1/2* Gene Mutations and Increased Risk of Breast and Ovarian Cancer

Breast and ovarian cancers are the first and fifth most common causes of cancer death in women.[1] Hereditary forms account for 5 – 10 % of all cases diagnosed, with germline mutations in *BRCA1* or *BRCA2* genes being associated with increased risk of breast and ovarian cancer.[2] For ovarian cancer specifically, up to 18 % of all cases may be attributable to germline mutations in the *BRCA1* or *BRCA2* genes.[3] Somatic mutations in *BRCA1* and *BRCA2* also account for other *BRCA*-related cancers, although their precise contribution to the total number of cases diagnosed remains unknown.[4]

## *BRCA1/2* increases the lifetime risk of developing cancer[5]




The risk of developing breast cancer for any individual with a germline *BRCA1* or *BRCA2* pathogenic variant increases from 12 % to 46 – 87 % or 38 – 84 %, respectively, while the risk of developing ovarian cancer increases from 1 – 2 % to 39 – 63 % or 16.5 – 27 %, respectively.[5]

By detecting cancer early, patients can have timely access to preventative measures and proactive treatment – leading to a better overall prognosis. In addition, genetic results can also have implications for the patient´s family members and their respective cancer risks.

# When to Perform Germline *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 diagnosis at the age of ≤ 45 years[6]
- Multiple breast cancers, bilateral or ipsilateral[6]
- Breast and ovarian cancer at any age
- Male breast cancer[6]
- Triple-negative (estrogen receptor negative, progesterone receptor negative and HER2/neu negative) breast cancer diagnosed ≤ 60 years of age
- Pancreatic cancer at any age[1]
- Two or more relatives with breast cancer, one under the age of 50
- Three or more relatives with breast cancer at any age
- A previously identified *BRCA1* or *BRCA2* mutation in the family[6]
- Personal history of breast cancer between the age of 46 – 50 and a close family member with breast, ovarian, pancreatic or prostate cancer[6]
- Personal history of breast cancer at any age and a close family member with breast cancer at age 50 or younger, or two or more close family members with breast cancer at any age[6]
- Metastatic prostate cancer at any age[6]

## When to Perform Somatic *BRCA1/2* Testing

If a patient has been diagnosed with cancer, and germline testing is negative, somatic testing of the *BRCA1/2* genes is still highly beneficial and can significantly improve the prognosis and quality of life. Somatic mutation analysis of tumors can identify therapeutic sensitizing and resistance mutations. This enables a more detailed assessment of the diagnosis and prognosis and 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.

## What Are the Possible Outcomes of the Test?

### 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 over their lifetime.

### Negative

A negative test result should be evaluated depending on the personal and family medical history of the tested individual, and whether or not a harmful variant has already been identified in the family. A negative test result should be discussed with your physician to understand which individual cancer screening prevention programs might be appropriate for the patient or if aditional genetic testing should be performed.

# Determining Next Steps

### 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.

When 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

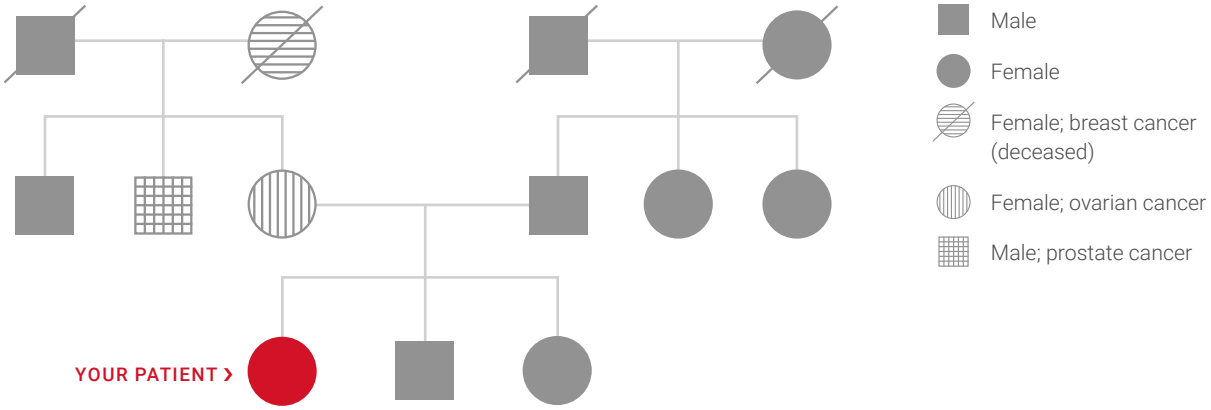
If no mutation in *BRCA1* or *BRCA2* is identified, the following explanations must be considered:

- The case is not due to an inherited *BRCA1/2* variant, but is a sporadic case
- The causative mutation is in an intron, or in a regulatory element that cannot be identified with routine diagnostic methods[7]
- Other genes and disorders associated 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 such as CentoBreast®, CentoCancer®, or CentoCancer® comprehensive.

# Case Study

Clinical Overview: Female patient, 35 years old. No breast pain and no mass in the clinical examination. Regular menstrual cycles. Use of oral contraceptives pills for five years. Patient is interested in starting a family and knowing her cancer risk before planning her second pregnancy. Family history: one first degree relative with ovarian cancer (diagnosed before age 50), one first degree relative with prostate cancer, and one 2nd degree relative with bilateral breast cancer (diagnosed before age 50).




The probability of identifying a *BRCA1/2* mutation in the patient is high because of her family history. *BRCA1/2* germline testing is recommended.

- Identification of a pathogenic variant would confirm the significantly increased lifetime risk of developing breast and ovarian cancer
- Genetic counselling, individualized surveillance and potential therapy options must be discussed with the patient and/or sibilings

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.

# *BRCA1/2* Testing at CENTOGENE

CENTOGENE offers *BRCA1/2* breast cancer testing to identify potentially harmful mutations in *BRCA1/2* genes that could be associated with increased risk of cancer in family members. The test can be performed in 15 days with a minimal sample amount.

DNA is analyzed from a blood or tissue sample. CENTOGENE can perform germline genetic testing from dried blood spots collected on an easy-to-use filter cards (CentoCard®). 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.

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.

## *BRCA1, BRCA2* Panel

| | |
|---|---|
| **Turnaround Time** | 15 days |
| **Coverage** | ≥ 99.5 % of target region covered ≥ 20 x |
| **Type** | Germline |
| **Details** | Next Generation Sequencing |
| **Required Material** | ≥ 1 filtercard |

## *BRCA1, BRCA2* Panel Combi

| | |
|---|---|
| **Turnaround Time** | 15 days |
| **Coverage** | ≥ 99.5 % of target region covered ≥ 20 x |
| **Type** | Germline |
| **Details** | Next Generation Sequencing + Deletion / Duplication (MLPA Analysis) |
| **Required Material** | ≥ 1 filtercard |

## *BRCA1, BRCA2* Panel Plus

| | |
|---|---|
| **Turnaround Time** | 15 days |
| **Coverage** | ≥99.5% of target region covered ≥20x |
| **Type** | Germline |
| **Details** | Next Generation Sequencing + Deletion/Duplication (NGS-Based CNV Analysis) |
| **Required Material** | ≥1 filtercard |

## *BRCA1, BRCA2* Somatic Mutation Analysis

| | |
|---|---|
| **Turnaround Time** | 10 days |
| **Coverage** | ≥97% ≥200x |
| **Type** | Somatic |
| **Details** | Next Generation Sequencing |
| **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 |

## Deletion/Duplication Testing

| | |
|---|---|
| **Turnaround Time** | 15 days |
| **Type** | Germline |
| **Details** | Deletion/Duplication (MLPA Analysis) |
| **Required Material** | ≥1 filtercard |

# The CENTOGENE Advantage

**MORE THAN TARGETED BREAST CANCER SCREENING. THE SUPPORT YOU NEED TODAY.**

## CentoCard®

Our quick, cost-effective, and hassle-free solution for shipment of clinical blood samples for genetic testing. CentoCard® provides a single sample for complete patient diagnostics: enzyme assay, biomarker analysis, and genetic testing.

## Extended Phenotyping

Structuring your patient's symptoms into Human Phenotype Ontology (HPO) terms ensures the best quality of clinical information for data interpretation.

## Data Safety and Research Use

With transparent and easy-to-understand consent forms, your patients can make educated decisions without worrying about data protection. By consenting to the research and storage option, you and your patients will advance research, the understanding of rare diseases, and the quality of future diagnoses and therapies.

## Multiomics Testing

Continuous research identifies and validates biomarkers, increasing disease understanding and enabling therapy monitoring. This has already added diagnostic certainty to lysosomal storage disorders and other diseases.

## CentoPortal®

Our user-friendly and fully-secure online service **www.centoportal.com** is designed to assist in ordering tests, transferring patient data, administering patient's samples, and accessing your diagnostic reports 24/7.

## Bio/Databank

Our rare disease-centric Bio/Databank with over half a million patients and more than 30 million unique variants enable world-class medical interpretation.

## Clinical Studies and Pharma Partnerships

By participating in clinical studies, your patients benefit as they foster the development of new therapies and improved monitoring. Through pharmaceutical partnerships, we also leverage our expertise to speed up drug development in rare diseases.

## World-Class Expertise

CENTOGENE's reputation is built on an international team of genetic and bioinformatics experts, the latest lab technology, continuously improved processes and protocols, and unique data analysis software.


1 Easton DF, et al. Breast and ovarian cancer incidence in BRCA1- mutation carriers. Breast Cancer Linkage Consortium. Am J Hum Genet. 1995 56:265-71.

2 Edlich et al. Breast cancer and ovarian cancer genetics. J Long Term Eff Med Implants. 2005;15(5):533-45. Review.

3 Alldredge J, Randall L. Germline and Somatic Tumor Testing in Gynecologic Cancer Care. Obstet Gynecol Clin North Am. 2019;46(1):37-53. doi:10.1016/j.ogc.2018.09.003

4 Tung N, Garber J. BRCA1/2 testing: therapeutic implications for breast cancer management. British Journal of Cancer. 2018.

5 Petrucelli et al. BRCA1- and BRCA2- Associated Hereditary Breast and Ovarian Cancer. In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. 1998 Sep 4 [Updated 2016 Dec 15].

6 According to the Evidence-Based Cancer Guidelines, National Comprehensive Cancer Network (NCCN).

7 Variants of uncertain significance are not reported.

... for a patients' better tomorrow.

Please visit our website for more information:
**www.centogene.com**

## CONTACT DETAILS

**CENTOGENE GmbH**
Am Strande 7
18055 Rostock
Germany

CENTOGENE GmbH is a subsidiary of CENTOGENE N.V.

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

Rostock - CLIA #99D2049715

Cambridge - CLIA #22D2154474

V5.1eng_July2021