CENTOGENE

THE RARE DISEASE COMPANY

BRCA 1/2

Breast cancer testing at CENTOGENE

Think about tomorrow, today.

Thinking about tomorrow, today.

Caring for people through reliable genetic testing.

Helping your patients and their families to make decisions about their therapy and screening options.

Bridging genetic testing and medical expertise in breast cancer testing

CENTOGENE is a global leader in the diagnosis of rare genetic diseases and holds multiple international accreditations (ISO, CAP, CLIA), meeting the highest standards for diagnostic testing and reporting. Our experience combined with our scientific expertise and medical competence allows the application of state-of-the-art technologies and the development of a unique, multi-ethnic mutation database, CentoMD®.

Over the past years, CENTOGENE has analyzed thousands of BRCA patients from all over the world. This medical expertise enables CENTOGENE to provide you and your patients with reliable interpretation results.

In the following, you will find detailed information regarding the different approaches that are used to perform molecular diagnostics for breast cancer at CENTOGENE.

Contact us today to gain further insight into your individual genetic disease cases.

Prof. Arndt Rolfs, MD
Chief Executive Officer

General information

Prevalence of breast cancer

Breast cancer accounts for approximately 25% of all cancers diagnosed in women. The hereditary form of breast/ovarian cancer accounts for 5-10% of all cases and is clearly associated with mutations in the BRCA 1/2 genes.

Mutations in the BRCA genes cause a genetic predisposition for a patient of 50-85%. Breast cancer risk is associated with a number of risk factors including female gender, age, Caucasian ethnicity, excess weight and increased height, hormone therapy after menopause, radiation therapy, early menarche, late menopause, no or late first birth, alcohol consumption, benign breast conditions, exposure to certain environmental substances (organ chlorines, tobacco).

However, the strongest risk known today is a genetic predisposition due to changes in breast cancer associated genes. 5-8% are associated with inherited gene mutations and breast cancer cluster in affected families. These cancers are described as hereditary breast cancers and tend to develop earlier in life than sporadic cases, and new primary tumors are more likely to develop in both breasts.

Role of BRCA 1/2

The BRCA 1/2 genes are tumor suppressor genes which repair DNA damage. They lose their function when mutations occur, which can promote cancer.

Mutations in the BRCA 1/2 genes are inherited in an autosomal dominant pattern and are highly penetrant. Carrying an inherited mutation in either BRCA 1 or 2 significantly increases the risk of breast cancer in both women and men (for age ~ 30 years from 3.2% up to 85% for age ~ 70 years).

By detecting cancer early, your patient will have access to preventative measures and proactive treatment – leading to an overall better prognosis.

Genes involved in hereditary breast/ovarian cancer

- >2,600 mutations in:
  - BRCA1 – chromosome 17
  - BRCA2 – chromosome 13
- Autosomal dominant transmission
- Carrier frequency of BRCA 1/2 mutations
  - ~1/500 – 1/1,000 in general (Caucasian) population
  - 1/40 – 1/50 in Ashkenazi Jewish people (3 common mutations in Ashkenazi Jews)
  - Unique French Canadian mutations

Consequences of having a BRCA mutation

Estimated cancer risk by age 70

Genes	BRCA mutation carriers	General population
Breast cancer BRCA 1/2 ♀	85 %	11 %
Ovarian cancer BRCA1	40 – 60 %	1 – 2 %
Ovarian cancer BRCA2	10 – 20 %	1 – 2 %
Breast cancer BRCA2 ♂	≤ 6 %	Rare

When to test for BRCA 1/2 mutations

We suspect a mutation in BRCA1 or BRCA2 and recommend testing, 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*
- Both 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 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 strongly encourages that all genetic testing is accompanied by qualified genetic counseling before and after the test.

*according to the Evidence-Based Cancer Guidelines, National Comprehensive Cancer Network (NCCN).

Management

Treatment of breast and ovarian cancer in cases with **BRCA 1/2** mutations is similar to that of sporadic forms. However, new drugs that specifically target the **BRCA 1/2** signaling pathways are approved.

One high impact on the patient and the family is the possibility to prevent primary manifestations. If a woman carries a BRCA 1/2 mutation, prophylactic mastectomy and/or oophorectomy and chemoprevention using tamoxifen may be suggested by the gynecologist. If such invasive procedures are not an option, surveillance is highly recommended. Breast cancer screening in women and men relies on a combination of monthly breast self-examination, annual or semiannual clinical breast examination, annual mammography, and breast MRI. Annual pelvic ultrasound and/or CA-125 concentration has not been effective in detecting early-stage ovarian cancer.

Once a germline mutation in BRCA 1/2 has been identified in a family, testing of at-risk relatives can identify those family members who also have the familial mutation and thus need increased preventive actions. Germline mutations in BRCA 1/2 are inherited in an autosomal dominant manner. This means that each offspring of an individual with a mutation has a 50% chance of inheriting the mutation. Persons with an increased risk due to inherited mutations inbreast cancer genes should be offered additional programs according to guidelines and the associated risk for breast and eventually other associated tumors.

Patients with a significantly increased breast cancer risk due to an inherited variant should be informed about possibilities of individual risk reduction. Apart from avoidence of toxic substances such as tobacco and alcohol, regulation of optimal body weight and physical activity also bilateral prophylactic mastectomy and bilateral prophylactic salpingooophorectomy can be discussed.

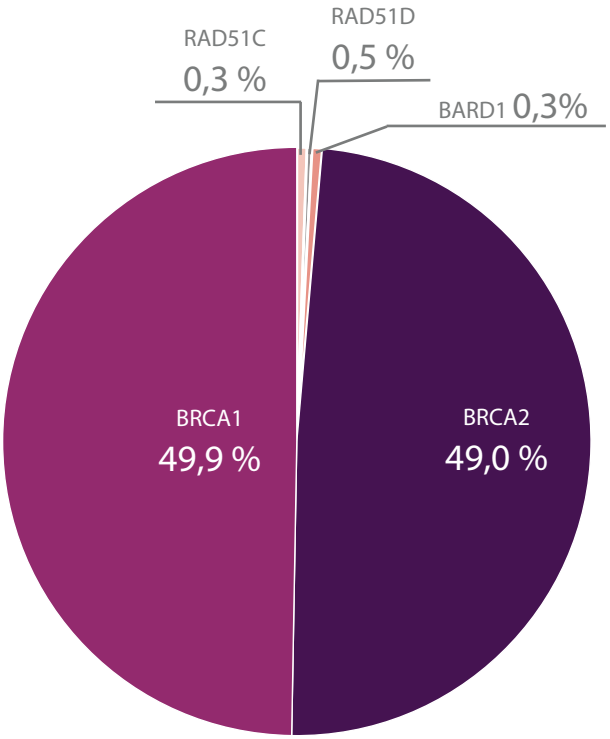
Therapies specifically targeted to the BRCA1 and/or BRCA2 pathways are approved. Knowing the carrier status of an affected or healthy person has a high impact on preventive procedures that can be performed and that increase life expectancy and quality.

Differential Diagnosis

If no mutation in BRCA1 or BRCA2 is identified, the following reasons may be considered:

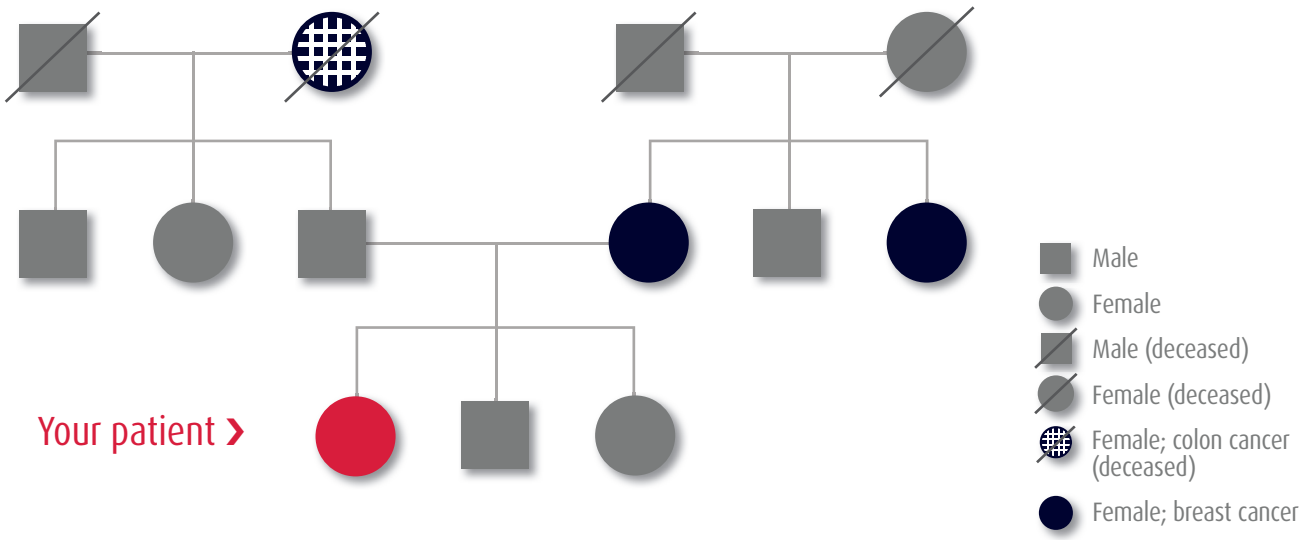
- **The case is not due to a mutation, but is a sporadic case (risk of breast cancer is 12%)**
- **Other disorders with elevated risk of breast and/or ovarian carcinoma should be considered, such as:**
  - **Li-Fraumeni syndrome (LFS):** a cancer predisposition syndrome associate with the development of soft tissue sarcoma, osteosarcoma, pre-menopausal breast cancer, brain tumors, adrenocortical carcinoma (ACC), and leukemias. At least 70% of individuals diagnosed clinically have an identifiable germline mutation in **TP53**. **The CHEK2 variant c.1100delC:** confers an approximately two - to threefold increase in risk of breast cancer in women and a tenfold increase in men.
  - **Cowden syndrome (CS):** one of the phenotypes in **PTEN** hamartoma tumor syndrome (PHTS). CS is a multiple hamartoma syndrome with a high risk of benign and malinant tumors of the thyroid, breast, and endometrium. A diagnosis of PHTS is only made when a **PTEN** mutation is identified.
  - **Hereditary diffuse gastric cancer (HDGC):** susceptibility for diffuse gastric cancer and lobular breast cancer (risk of up to 50%).
  - **Peutz-Jeghers-type hamartomatous polyps:** characterized by hamartomatous polyps in the small intestine and an elevated risk of breast cancer (32% by age 60) is characterized by the association of gastrointestinal polyposis and mucocutaneous pigmentation. Pathogenic variants in **STK11** (LKB1) are identified in a significant proportion of patients.
- **The causative mutation is located in an intron or in a regulatory element and cannot be tested or evaluated using routine diagnostic methods**

Overview of cases identified at CENTOGENE to carry mutations in genes related to breast cancer (in %)



Case illustration: Moderate risk for hereditary breast cancer

Two 1st/2nd degree relatives on the same side of the family with breast cancer < age 70.

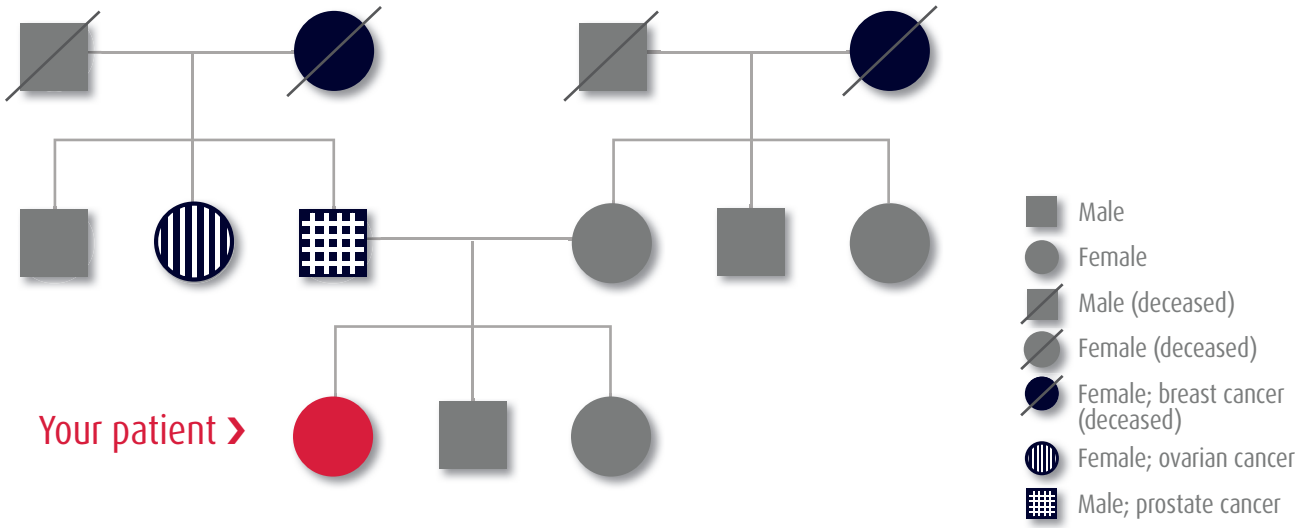


Management

- Complete a family cancer history including any breast or ovarian cancer in any 1st or 2nd degree female or male relative on either side of the family
- Update the family history and review risk triage on a regular basis
- Discuss lifestyle changes
- Consider prospective staging and potential therapy options following international guidelines

Case illustration: High risk for hereditary breast/ovarian cancer

One 1st/2nd degree relative with
- Bilateral breast cancer, first one before age 50
- Ovarian cancer (any age)



Management

- Complete a family cancer history including any breast or ovarian cancer in any 1st or 2nd degree female or male relative on either side of the family
- Update the family history and review risk triage on a regular basis
- Detailed clinical examination, with all the imaging and laboratory tests
- Offer genetics or familial cancer clinic referral
- Consider prospective staging and potential therapy options following international guidelines

Please visit our website
for more information:

www.centogene.com

Contact details:

Centogene AG
Doreen Niemann
Senior Director Marketing & Sales
Schillingallee 68
18057 Rostock
Germany

Email: doreen.niemann@centogene.com
Phone: +49 (0)381 203 652 - 181
Fax: +49 (0)381 203652 - 19

ISO/EN 15189
CLIA #99D2049715

DAkkS
Deutsche
Akkreditierungsstelle
D-ML-19386-02-01

cap ACCREDITED™

V3_August_2015