CENTOGENE
THE RARE DISEASE COMPANY

CentoBreast®

Knowledge today.
Action tomorrow.

Working together ...

CentoBreast® – Breast and Ovarian Cancer Testing

Approximately 1 in 8 women will be diagnosed with invasive breast cancer.[1] Breast cancer risk is associated with several risk factors, including female gender, age, race / ethnicity, excess body weight, exposure to hormone therapy, alcohol consumption, smoking, family or personal history, and genetic predisposition among others.[1,2] **One of the strongest risk factors is genetic predisposition with mutations in inherited genes** accounting for 5% to 10% of all breast cancers.

BRCA1 and *BRCA2* mutations are the most common causes of hereditary breast and ovarian cancers. In the general population, about 12% of women will develop breast cancer in their lifetime, whereas women with pathogenic variants in *BRCA1* and *BRCA2* will have an increased risk of malignancy of 46 – 87% and 38 – 84%, respectively.[3] Mutations in *BRCA1* or *BRCA2* account for 30% of hereditary breast cancer, however, other genes such as *CDH1*, *CHEK2*, *PALB2*, *PTEN*, and *TP53*, can also contribute to the risk of breast/ovarian cancer (see table 1).[4]

CentoBreast has been designed to test for a wide range of genes implicated with breast and ovarian cancer as well as to test genes for differential diagnosis from other susceptibility syndromes, such as Lynch, Codwen, Peutz-Jeghers, and Li-Fraumeni syndromes. The correct profiling of mutations in breast and ovarian cancer genes represents a fundamental step in the diagnosis and treatment of these malignancies.

Breast Cancer: Clinical Features

The first symptoms that may appear as a presentation of breast cancer include:

- Palpable lumps in breast or axillary region
  (specially hard, with focal nodularity, asymmetry with the other breast, fixation to skin or muscle)
- Thick or firm tissue in or near the breast or under the arm
- A change in the size or shape of the breast
- Nipple discharge (fluid that is not breast milk)
- Nipple changes, such as inverted nipple
- Changes to the breast skin, areola, or nipple (itching, redness, scaling)

Screening Options

Early detection of breast cancer significantly prolongs survival prospects and offers many opportunities for early treatment or management. Apart from generally recommended breast cancer prevention actions, people with an increased risk due to inherited mutations in breast cancer genes should consider genetic testing to estimate their risk for breast and other associated tumors.

Because of regular screening and examinations, breast cancer can often be found before a woman has any physical symptoms. With new technologies and genetic testing tools, as well as breast cancer screening (e.g., mammograms), the survival rate of breast cancer affected women is now significantly higher than in previous years.

Additionally, genetic testing can provide valuable information for the best therapeutic approach. For example, PARP inhibitors have been shown to be especially effective in patients with *BRCA1* or *BRCA2* mutations.[4] Identification of the type of variant can help pinpoint the responsiveness of the cancer to a respective treatment and hence aid in the selection for the best therapy for the patient.

Who Should be Considered for Genetic Testing with CentoBreast?

You should consider being tested if you are are at risk of being affected by early breast cancer or ovarian cancer (any age) or pancreatic cancer, metastatic breast cancer, or metastatic prostate cancer. At-risk patients include those who may be affected by the following criteria:[5]

- Female breast cancer diagnosed at 45 years or younger (or any age if Ashkenazi Jewish)
- Male breast cancer or family history
- Triple negative breast cancer diagnosed < 60 years of age (estrogen receptor negative, progesterone receptor negative, and HER2 / neu negative)
- Two or more primary breast cancers, the first diagnosed < 50 years
- Invasive ovarian or fallopian tube cancer, or primary peritoneal cancer
- Exocrine pancreatic cancer
- Metastatic prostate cancer
- Breast cancer at any age and a relative with breast cancer diagnosed ≤ 50 years, or any of the cancers listed above
- A previous pathogenic variant identified from tumor genomic analysis, regardless of tumor type if high suspicion for germline origin and confirmation of germline status has clinical implications for the patient or family members
- Non-affected individuals with a family history of any of the criteria above mentioned

CENTOGENE recommends that all genetic testing is conducted together with pre- and post-test counseling by a qualified genetic counselor, medical geneticist, or physician.

Key Features and Performance

COVERAGE	• All coding regions of 30 genes and +/-10 bp exon/intron boundaries • ≥ 99.5 % targeted regions covered at ≥ 20 x • For each gene, all SNVs described in HGMD and Bio / Databank are covered
VARIANT TYPES	• Sensitivity: SNVs and InDels (≤ 50 bp) > 99.2 % CNVs ≥ 3 exons > 93.8 % • Accuracy of > 99.9 % • Specificity of ≥ 99.9 % guaranteed for all reported variant. Variants with low quality and/or unclear zygosity are confirmed by orthogonal methods (Sanger, MLPA, qPCR)
TAT	15 business days
REQUESTED MATERIAL	≥ 1 µg DNA or 1 ml bone marrow or 1 ml blood or 1 filter card (CentoCard®)
REPORTING	Pathogenic and likely pathogenic variants are reported following American College of Medical Genetics and Genomics (ACMG) classification guidelines.
DELETION / DUPLICATION	High resolution NGS-based CNV analysis to detect larger deletions and duplications is included in all our panels at no extra cost. Deletion/duplications constitute 5 – 10 % of disease-causing variants. By including CNV analysis in our panels, the potential of providing the most accurate diagnosis increases.
IMPROVED INTERPRETATION	Our Bio / Databank enables access to more than **30 million unique variants** for best medical interpretation.
VARIANT RECLASSIFICATION PROGRAM	All our panels are automatically entered into our variant reclassification program. This program supports the identification of new genetic evidence, and physicians will be notified free of charge for life if the nature of a previous diagnosis has been impacted.

What Are the Possible Outcomes of the Test?

Positive

If no cancer has been confirmed and 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.

For patients with cancer, a positive result might affect treatment decisions, and these patients with a significantly increased breast cancer risk due to an inherited variant should be informed about possibilities of individual risk reduction.

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. Variants of uncertain significance are reported as a negative result.

Patients with a significantly increased breast cancer risk due to an inherited variant should be informed about possibilities of individual risk reduction. Apart from specific patient tailored surveillance based on guidelines and avoidance of toxic substances, such as tobacco and alcohol, regulation of optimal body weight and physical activity, prophylactic mastectomy or salpingo-oophorectomy, as well as hormonal therapy and can be discussed. salpingo-oophorectomy can be discussed.

CentoBreast – Panel Composition

Genes	Associated cancers
ABRAXAS1	Mutations in this gene are associated with hereditary predisposition to breast cancer [1,6]
ATM	Lifetime breast cancer risk of 17 – 25% [2,7]
BARD1	Low / moderate breast cancer risk gene [3,8]
BRCA1	**Risk for Malignancy of 46 – 87% for breast cancer and 39 – 63% for ovarian cancer [2,7]**
BRCA2	**Risk for Malignancy of 38 – 84% for breast cancer and 16.5 – 27% for ovarian cancer [2,7]**
BRIP1	Low / moderate breast cancer risk gene that codes for *BRCA1* interactin protein 1 [3,8]
CDH1	Lifetime breast cancer risk of 39 – 52% [2,7]
CHEK2	**Lifetime breast cancer risk of 25 – 39% [2,7]**
DICER1	Germline mutations in *DICER1* have been associated with breast invasive carcinoma [5,9]
EPCAM	Ovarian cancer [2,7], Lynch syndrome
FANCC	Proposed as a breast cancer susceptibility gene [6,10]
MEN1	Associated with an early-onset elevated breast cancer risk [7,11]
MLH1	Ovarian cancer [2,7], Lynch syndrome
MRE11	The *MRE11-RAD50-NBS1* complex mantains genomic integrity and mutations in genes from this complex have been associated with breast and / or ovarian cancer [8,12]
MSH2	Ovarian cancer [2,7], Lynch syndrome
MSH6	Ovarian cancer [2,7], Lynch syndrome
MUTYH	Monoallelic carriers increased risk of breast cancer and mutation carriers increased risk of develping urinary bladder and ovarian cancers [9,13]
NBN	Mutations associated with breast and / or ovarian cancer [8,12]
PALB2	Lifetime breast cancer risk ≤ 58% [2,7]
PMS1	Mutations in gene associated with breast invasive ductal carcinoma [11,14]
PMS2	Ovarian cancer [7], Lynch syndrome
PTEN	**Lifetime breast cancer risk 25 – 50%, may be ≤ 85% [7], Cowden-syndrome**
RAD50	Mutations associated with breast and/or ovarian cancer [12]
RAD51C	Ovarian cancer [2,7]
RAD51D	Ovarian cancer [2,7]
RECQL	Breast cancer susceptibility gene [12,15]
SMARCA4	Mutations predisposed to small cell carcinoma of the ovary [13,16]
STK11	Lifetime breast cancer risk 32 – 54% and ovarian (mostly SCTATs [20]) [2,7], Peutz-Jeghers syndrome
TP53	**Lifetime breast cancer risk ≤ 79% (often pre-menopausal) [2,7], Li-Fraumeni syndrome**
XRCC2	Proposed that mutations in the *XRCC2* gene might affect susceptibility to, and survival from, breast cancer [14,17]

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2 http://www.Breastcancer.org

3 https://www.ncbi.nlm.nih.gov/books/NBK1247/

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

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The CENTOGENE Advantage

MORE THAN 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.

... for a patients' better tomorrow.

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

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