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References

(1) Arbeitsgemeinschaft Bevölkerungsbezogener Krebsregister in Deutschland, in Zusammenarbeit mit Robert Koch Institut: "Krebs in Deutschland, Häufigkeiten und Trends", 5. erweiterte aktualisierte Auflage (Saarbrücken 2006).

(2) Ponder B: Genetic testing for cancer risk. Science 278:1050-1054 (1997).

(3) Bowcock A: Breast Cancer Genes. Breast Vol 3: 1-6 (1997).

(4) Recommendations according to a special program of the German Krebshilfe "Familial Breast and Ovarian Cancer" (www.krebshilfe.de).

(5) Statement of the American Society of Clinical Oncology: genetic testing for cancer susceptibility, Adopted on February 20, 1996. J. Clin. Oncol. 14(5):1730-6 (1996).

(6) http://www.bioscientia.de/dataFile/bioscientiaDeDe/File/BRCABroschuere2005.pdf

(7) Berufsverband Medizinische Genetik e.V., Deutsche Gesellschaft für Humangenetik, Leitlinien zur Erbringung molekulargenetischer Leistungen: 4. Leitlinien zur molekulargenetischen Labordiagnostik. medgen 8: Heft 3, Sonderbeilage S. 4 (1996).

General information

Genetic counselling: it is strongly recommended that the decision for or against molecular genetic *BRCA* analysis, transfer of reports and interpretation of test results is accompanied by qualified genetic counselling of the patient.

An informed consent signed by the patient, a questionnaire of family history, as well as confirmation of payment transfer, must be included with each sample. Relevant documents can be downloaded from our web site or sent by mail on request.

Forms
Molecular genetic diagnostics

Sample material
2 samples with 10 ml each of EDTA-blood (closed system such as Vacutainer® or Monovettes®)
Send the sample at room temperature within maximal 3 days after blood sampling.

Analysis time
4-6 weeks after receipt

Results
The final report contains detailed interpretation of the test result. If and whenever there is a change in the clinical interpretation of a specific reported variant, an amended report will automatically be provided by Bioscientia. Therefore all reports will always be updated according to the latest scientific standards.
Anonymity of the test result is guaranteed. Results will only be reported to the patient's physician. Comparison with existing data bases will only be performed by anonymization of personal data.

Accredited by
Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten
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Genetic testing for hereditary breast and ovarian cancer

BRCA1 and *2* analysis

Scientific background

Breast cancer is one of the most prevalent cancers in women. The incidence of breast cancer has increased in Europe over the past 20 years, particularly among younger women. In Germany about 55,000 new cases are reported each year and approximately 18,000 women die due to this form of cancer in this interval (1).

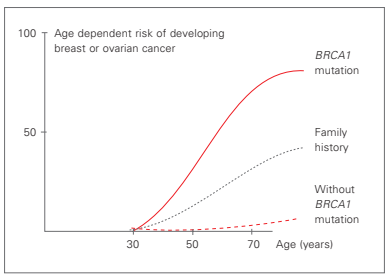

Fig. 1:
Probability in percent for the development of a carcinoma in relation to age, in presence of a mutation *(BRCA1)*, a positive family history, or in absence of a specific mutation. Reprinted with permission (2).

Genetic and non-genetic factors contribute to the development of breast cancer. From the age of 40 onwards a considerable increase for the disease risk can be observed (Figure 1). Women without affected family members have a probability of 10 % to develop breast cancer.

An accumulated occurrence of breast cancer in single families is indicative of a stronger genetic component. Besides occurrence of bilateral breast carcinoma in several consecutive generations within a family, the age of first diagnosis is the most important criteria for a genetic predisposition. For example, when the age of the patient at diagnosis is significantly below 40, the probability of a causative genetic factor is increased. Familial appearance of breast carcinomas is observed in up to 25 % of all cases (3). In 5 - 10 % of affected persons alterations in the genes *BRCA1* and *BRCA2* are the cause of the disease. In addition to the risk of developing breast cancer, carriers of a *BRCA* mutation have, compared to control groups, a 10-fold increased risk for ovarian cancer. Since in up to 80 % of hereditary breast carcinomas *BRCA1* und *BRCA2* are involved in the disease process, a molecular genetic analysis of these genes can be offered to individuals with an increased risk. In order to decide whether an indication to perform genetic testing is given, individual risks can be estimated according to national and international recommendations. These take into account clinical records and family history (see Box 1).

- ≥ 2 affected individuals with breast or ovarian cancer, with 1 individual affected < 50 years. Age of disease onset is of minor importance in families with 3 or more affected individuals
- 1 affected individual with unilateral breast cancer, age ≤ 30 years
- 1 affected individual with bilateral breast cancer, age ≤ 40 years
- 1 affected individual with ovarian cancer, age ≤ 40 years, or 1 affected individual with breast and ovarian cancer
- 1 male affected with breast cancer
- Individuals with an estimated risk of > 10 %

Box 1:
Indications for gene analyses of *BRCA1* and *BRCA2* (4, 5).
There are various methods to estimate or calculate disease risks.
For further information see also (6).

Molecular analysis of *BRCA1* and *BRCA2*

The molecular genetic analysis of *BRCA1* and *BRCA2* is the only method to identify patients as mutation carriers. It should be noted that the result of such a molecular diagnostic test may have special consequences for the patient. Therefore it is recommended that this test as well as any other molecular diagnostic test should always be accompanied by genetic counselling (7). In such a setting the patient will be provided with detailed information about possibilities, limitations, potential benefits and risks of this procedure. Supported by counselling, the patient can decide whether genetic testing is to be performed or not ("informed consent").

Comprehensive sequence analysis of *BRCA1* and *BRCA2* and detection of large genomic rearrangements applying the new BART assay guarantees an as yet unsurpassed quality standard.

Diagnostic service in detail

- Comprehensive sequence analysis of the *BRCA1* and *BRCA2* genes. This covers all coding exons including the exon flanking regions, in total more than 17,000 bp. Due to the optimal technical resources with more than 40 automated DNA sequencers, results are generally reported within 4 to 6 weeks. In case of a positive mutation result, this includes a second independent replication of the finding.
- In case of a mutation negative sequencing result of *BRCA1* and *BRCA2*, the **B**RCA **A**nalysis **R**earrangement **T**est (**BART assay**) will be performed. The BART assay allows the detection of any large genomic rearrangement in *BRCA1* and *BRCA2*. Such large genomic rearrangements occur in a small percentage (1 %) of patients tested for hereditary breast and ovarian cancer (HBOC). The BART assay will be automatically performed at no extra charge for those patients being at high risk for HBOC, i.e. if they meet defined clinical criteria.
- Detailed final report and interpretation of the results with citation of the relevant scientific references.
- For the detection of unclassified variants (UVs), reports are regularly updated based upon new entries in national and international data bases. In case of a re-evaluation of a result, an amended report will be generated. Thus, all reported findings are updated according to the latest scientific standards.
- Scientific data transfer: in order to allow an active exchange of expert knowledge within the international scientific community, test results will be provided as data base entries in an anonymized form. This is accomplished while still ensuring strict data protection.