Breast cancer is the most common cancer occurring in women. It is estimated that about 1/8 women will develop breast cancer in their lifetime. There are two main types of breast cancer, occurring in the ducts or the lobes of the breast, while in rare cases the tumor may occur in other parts of the breast. Also, breast cancer may be metastatic or non-metastatic (in situ).

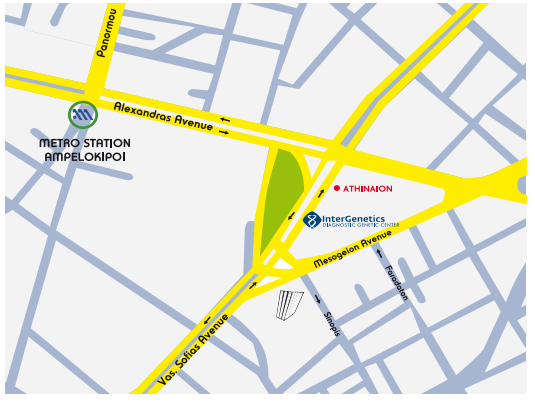
Furthermore, some types of breast cancer are sensitive to estrogen, meaning that estrogens promote tumor growth in the breast.

The treatments currently applied depend on the type and stage of the cancer and include chemotherapy, radiation and/or surgery (e.g. mastectomy). Overall, new developments have led to significant advances in treatment, especially when diagnosis is made at an early stage.

Like most cancers, breast cancer is a complex, multifactorial disease in which there is a strong interaction between genetic and environmental factors.

Approximately 5-10% of breast cancer is thought to be due to a specific hereditary cause and an additional 20-30% is estimated to be familial, meaning that it appears with greater incidence in a family compared to the general population. Hereditary breast cancer tends to occur earlier in life than non-hereditary sporadic cases and is most likely to involve both breasts.

Other risk factors for breast cancer include age, sex, reproductive history, alcohol, radiation, high body mass index and benign breast disease (such as atypical hyperplasia, etc.)



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GENETIC AND GENOMIC TESTING OF BREAST CANCER

- ✓ *genetic testing was confined to the analysis of only two genes and often without a meaningful end result*
- ✓ *massive analysis through genomic testing of all genes known to be associated with the disease, leads in a single step to a substantial increase in diagnostic yield*

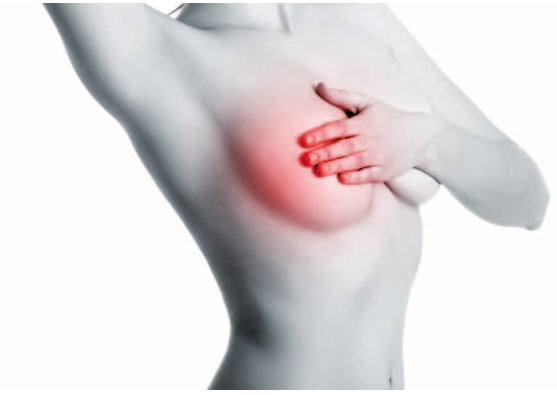
Breast cancer and the BRCA1 and BRCA2 genes

Mutations in the BRCA1 and BRCA2 genes predispose, i.e. are associated with an increased risk, for breast cancer, ovarian cancer but also other forms of cancer. Generally, the BRCA1 and BRCA2 genes are associated with 5-10% of all breast cancer cases. However, inherited mutations in these genes are detected in up to ~80% of familial forms of the disease (average 25-30%), i.e. when there is a family history of >2 affected members from the same side of the family and with age of onset of the disease at <50-55 years.

It is important to mention that specific international guidelines have been developed [e.g. American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network], which define both the genetic screening criteria specific to these two genes as well as the recommended actions depending on the test results. The mode of inheritance in the vast majority of cases is autosomal dominant, with variable expressivity and penetrance, meaning that individuals with mutations in either of these two genes will not necessarily develop the disease or will develop different type and gravity of symptoms.

Especially in the case of genetic testing of BRCA1 and BRCA2, there are no specific mutations which occur with high frequency in patients, with the possible exception of specific ethnic groups (e.g. Ashkenazi Jews). Given the increased importance of genetic testing and the heterogeneity of the disease, molecular genetic testing of mutations in these genes, which are both relatively large in size, should be as comprehensive as possible, covering all possible mutations through full DNA sequencing of the genes.

Therefore, screening for a few 'common" mutations of these two genes in the vast majority of cases is of no diagnostic value and is not recommended.



Genomic testing for breast cancer – exome sequencing of 19 genes associated with the disease

For many years, testing of the BRCA1 and BRCA2 genes was the fundamental genetic test in hereditary breast and ovarian cancer. While, as already mentioned, mutations in any of these two genes confer a considerable risk for breast cancer, recent studies have identified novel genes also associated with increased risk of breast cancer. Specifically, a group of 15-20 genes have been associated with up to 20% of hereditary breast cancer, and some of these genes are also associated with increased risk of other cancers, such as pancreatic cancer, ovarian cancer, and sarcomas. For example, the BARD1, BRIP1, NBN, RAD50 and RAD51C genes are involved in the mechanism of DNA repair (Fanconi anemia-BRCA pathway) through interaction with BRCA1 and BRCA2, and as a result mutations in any of these genes confers a 4-5 fold increased risk of breast cancer.

Therefore, the detection of possible mutations in multiple genes through simultaneous genomic analysis (which includes the BRCA1 and BRCA2 genes), is estimated to result in a 5-10 fold increase in the risk assessment for breast cancer.

How is genomic testing for breast cancer performed and how long does the test take to be completed

The test is based on the method of Next Generation Sequencing (NGS) and utilizes a special Genome Analyzer instrument together with complex and highly specialized software tools. The test is generally completed within 2-3 months.

Why is genomic testing for breast cancer useful

Understanding the genetic contribution to hereditary breast cancer provides us with very useful information concerning disease progression and family risk, both of which can vary depending on the molecular diagnosis. Knowing that a person has a particularly increased risk will help in effective medical management, such as the strategy and the age of onset for monitoring, as well as suggesting the necessary measures to reduce the risk of expressing the disease.

Genetic counseling

Proper clinical genetic assessment of each case and genetic counseling, both before and following the test, is essential in order to determine the appropriate strategy for laboratory testing and to interpret correctly the concepts of pathological and normal.