

Information Leaflet: BRCA 1/2 Gene Mutation Test For PARP Inhibitor

What are genes?

Normally each human cell has 23 pairs of chromosomes made up by DNA and proteins. Apart from sex chromosomes, there are 22 chromosomes in each pair, one of which is inherited from the father, and the other from the mother. Genes are a group of genetically encoded DNAs in chromosomes, which can control cell division, production, and function. However, when the genes are mutated, cells may proceed cell division and proliferation uncontrollably and may potentially become malignant tumors which affect other tissues of the body.

What are BRCA1 and BRCA2 genes?

BRCA1 (**BR**east **CA**nCer 1) and BRCA2 (**BR**east **CA**nCer 2) are genes associated with breast and ovarian cancer, located on the human chromosomes 17 and 13 respectively. Their function is to maintain the normal function of cells.

How mutations can occur in BRCA1/2 genes and what are the effects of mutations?

Mutations can occur either as somatic (non-hereditary) or germline (inherited from the family).

When there is a mutation in either the BRCA1 or BRCA2 gene, it will increase the risk of having hereditary breast and ovarian cancer syndrome (HBOCS) that will increase the risk of certain cancers, like breast or ovarian cancer in women. And they will usually present earlier than the normal population. Risk of other cancers including pancreatic cancer or melanoma (a type of skin cancer) will also increase for both sexes. It will also increase the risk of prostate cancer in male patients.

Ovarian Cancer Risks

The life-time risk of ovarian cancer is about 1.4% in women in the general population. According to the most recent literature, it was estimated that 39% of women who carried a BRCA1 mutation and 11% to 17% of women who carried a BRCA2 mutation would develop ovarian cancer by age 70 years.

Breast Cancer Risks

The life-time risk of breast cancer is about 12% in women in the general population. According to the most recent literature, it was estimated that 55% to 65% of women who carried a BRCA1 mutation and 45% of women who carried a BRCA2 mutation would develop breast cancer by age 70 years.

Reproductive Risk

People who had germline BRCA mutations have one copy of the faulty BRCA1/2 gene inside their bodies. They will have 50% chance (1 in 2 chance) of passing that faulty BRCA1/2 gene to each of their children. Those children with a faulty BRCA1/2 gene will have an increased risk of developing cancer.

What is genetic testing for BRCA1/2 mutations?

Genetic testing for BRCA1/2 mutations allows doctors to identify if the cancer is due to BRCA1 or BRCA2 mutations.

Patients could choose to undergo both blood BRCA1/2 (germline) mutation test and tumor BRCA1/2 (somatic) mutation test, or only tumor BRCA1/2 (somatic) mutation test. If a faulty BRCA1/2 gene is identified in cancer tissue only but not in blood (germline), it is most likely that the cancer is not due to HBOCS. On the other hand, if a faulty BRCA1/2 gene is identified in blood, it is highly probable that the cancer is caused by HBOCS.

If only tumor BRCA1/2 (somatic) mutation test is performed, there is a possibility of missing a small proportion (around 5%) of germline mutations and it is uncertain whether the disease-causing mutation(s) found (if any) is/are hereditary.

How will such genetic tests be done? Do I need to be hospitalized?

For a blood BRCA1/2 (germline) mutation test, it is done by taking a blood sample in the out-patient clinic. For patients who have undergone an allogeneic bone marrow transplant, blood samples are not suitable for blood BRCA1/2 (germline) mutation tests. Alternative samples including saliva or buccal mucosa swabs will be collected.

For a tumor BRCA1/2 (somatic) mutation test, it is done on the tumor tissue sample obtained during the previous operation procedure. Hospitalization is not required.

Test results take two to three months to be available.

What are the possible results of BRCA1/2 genetic testing and their meaning?

(i) Disease-causing mutation(s) was/were found: this indicates that the patient may be suitable for the specific targeted therapy. If disease-causing mutation(s) was/were detected in the blood sample (germline), it is highly probable that the patient is affected by HBOCS. If disease-causing mutation(s) was/were detected in the tumor tissue sample (somatic) only but not in the blood sample (germline), it indicates that the mutation is not hereditary. If the patient has only undergone tumor BRCA 1/2 (somatic) mutation test but not blood BRCA1/2 (germline) mutation test, there is a possibility of missing a small proportion (around 5%) of germline mutations and it is uncertain whether the disease-causing mutation(s) found is/are hereditary or not. Further clinical assessment and medical advice from specialist(s) is/are required on whether the patient is suitable for the specific targeted therapy.

(ii) No disease-causing mutation was found: this indicates that the molecular diagnosis of the gene being investigated was not confirmed or substantiated, and the patient is not suitable for the specific targeted therapy. It may be due to the absence of disease-causing mutations in the blood or/and tumor tissue, or due to limitations of current techniques or other unknown factor(s). However, the result does not totally exclude the possibility of BRCA1/2 gene mutations in patient's blood or/and tumor tissue samples.

(iii) Variant(s) of uncertain clinical significance (VUS): a mutation was found but whether this mutation will result in any disease or is just a benign polymorphism is uncertain with the latest medical genetic knowledge, and the patient may not be suitable for the specific targeted therapy. Polymorphism means the mutation is present in more than 1% of the general population that likely does not have harmful effects on health. When "VUS" was detected, genetic counseling and further genetic studies may be indicated. Nevertheless, a definitive conclusion may still not be made after the additional work up.

The results and interpretations in the test report are based on the current technology and knowledge. Future advances may provide further insight and possibly lead to a different understanding of the results. A new specimen may need to be provided if further testing is to be performed.

What are the benefits of BRCA1/2 genetic testing?

On an individual level, the genetic result can help clinicians make decisions about cancer treatments. For those patients found to have HBOCS, it also gives more information about the future risk of developing cancers, which enables clinicians to derive a tailor-made and comprehensive management plan.

Their first-degree relatives (including his/her parents, siblings and offsprings of both genders) may have a 50% chance of carrying the same mutation. Therefore, report results may reveal insights about your family members' health and genetic risk factors.

Individuals with disease-causing mutations or "VUS", and their first-degree relatives will be referred to a genetic counselling clinic for further follow-up.

What are the potential risks/implications of BRCA1/2 genetic testing to patient and family?

The results of blood BRCA1/2 (germline) mutation test may potentially affect you and/or your family members in terms of insurance applications, psychological or social issues. You are advised to take into consideration the possible effects of genetic test results before taking the test.

Do I need to tell family or other people about my test result?

The BRCA1/2 genetic testing result will only be released to you. There is no obligation to tell your family or others about the test result, but you are strongly encouraged to share such important information with your family. If the result cannot be released to you due to your incapacity or death, the blood BRCA1/2 (germline) mutation test result may be released to a nominated individual upon request within 3 months after the test result is available. Genetic test results are normally included in a person's medical records. Therefore, the results may become known to other people or organizations that have obtained authorized access to your medical records.