

HEREDITARY CANCER RISK TEST

About This Information Sheet

This information aims to help you decide whether to have a hereditary cancer risk test. Your healthcare provider will discuss this information with you and will ask you to sign a consent form before having the test.

This information sheet is in two parts:

PART 1: Understanding Your Test

Learn about genetic testing, how it works, and what to expect before your test.

PART 2: After Your Test

Find out about possible results, unexpected findings, and how your privacy is protected.

What are Mutations?

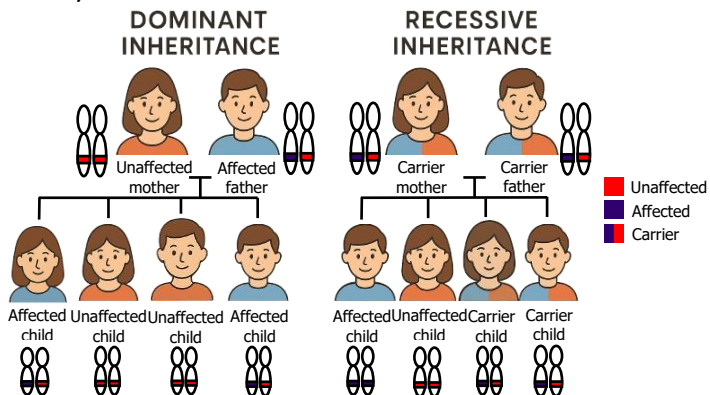
Genes are composed of DNA which encodes instructions telling cells how to function, grow, and develop. We all inherit approximately 20,000 pairs of genes from our parents which form an instruction manual, called a genome, which work together to create and operate all the different cell types in the human body. These instructions are passed from one cell to another during cell division.

Sometimes, errors or faults (typos and spelling mistakes) – also known as **mutations** - occur in these genes, often during DNA replication. Some are harmless and help create genetic diversity while others can be harmful and cause disease.

- When these errors arise during a person's lifetime, these acquired mutations are referred to as being of "somatic" origin.
- When these mutations are present in eggs or sperm, they are passed from parent to child. Such inherited mutations are referred to as being of "germline" origin.

Inheriting a mutation can predispose individuals to developing a genetic disease.

- Some mutations are strong and affect only one copy (inherited from the father or mother) – these are called "dominant mutations". Usually, a parent passing on a dominant mutation is affected with the disease.
- Some mutations are weak and only affect individuals who have inherited two faulty copies, one from each parent - these are called "recessive mutations." Parents passing on a recessive mutation are usually unaffected and are often termed "carriers".



Studying the pattern of inheritance of a disease within a family can help pinpoint the gene likely to be causing the inherited disease. A DNA test, however, is required to identify the causative mutation. Identifying the causative mutation in an affected individual and tracing its pattern of inheritance within a family can help establish the risk of other family members, including unborn individuals, developing the disease.

What is a Hereditary Cancer Risk Test?

Approximately 80 genes have been identified that increase the risk of humans developing cancer. Most of these are dominant genes while some are recessive. Families with a mutation in a dominant gene often have several affected individuals across multiple generations often with the same type of cancer. Families with a mutation in a recessive gene often only have occasional affected individuals so the pattern of inheritance may not be obvious.

Individuals from families with a higher-than-expected incidence of cancer, or particular cancer types known to be associated with inherited cancer syndromes, may seek a test to identify the causative gene and mutation. These patients are often referred by their doctor to a clinical geneticist or genetic counsellor who will often request a screening test.

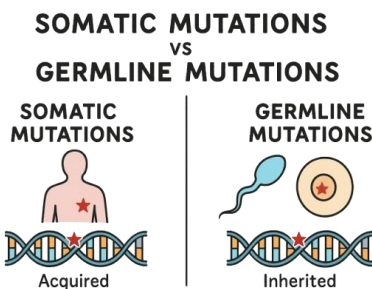
A hereditary cancer risk test screens for most cancer-predisposing genes known to increase the inherited risk of developing cancer. The test is performed on a blood, rather than a tumour, sample. DNA is extracted from the blood cells and is sequenced to reveal the DNA code for those genes presently known to predispose to cancer looking for a causative mutation. Identifying such a mutation can help establish or confirm a diagnosis of an inherited cancer syndrome.

Depending on the type of cancer, your doctor may request a broad panel to look at all or most cancer-predisposing genes or request a smaller panel with a limited number of genes or even a single gene test because the particular cancer type is associated with mutations in a set of genes or just one gene. In most cases, all or most of the known cancer-predisposing genes will be tested but only those genes identified by your doctor on the request form will be analysed and reported. The remaining information will be masked and not examined.

What is the Difference between a Hereditary Cancer Risk Test and a Cancer Somatic Gene Test?

Cancers are genetically complex and often contain many acquired somatic mutations. A single mutation, even an inherited one, is insufficient to cause cancer. Many additional somatic mutations are required to initiate and drive a cancer. Some of these are targets for various cancer treatments. These acquired mutations can be tested for using somatic gene tests.

Approximately 10% of all cancers have an underlying inherited basis which starts with inheriting a single mutation. This single germline mutation alone, however, is insufficient to cause cancer and requires a second acquired mutation in the other copy to start the process. By the time a cancer becomes clinically evident it often contains acquired mutations in many other cancer-associated genes.



Today, it is common to perform a somatic gene test on a person's tumour to identify which mutations are present in the tumour as these often guide treatment. These tests are usually requested by oncologists treating patients with advanced cancer. Most of the mutations identified in the tumour will be somatic. However, in approximately 10-18% of cases, a suspected germline mutation in a cancer-predisposing gene may also be identified.

In some cases, this will be unexpected as there may be no obvious family history of excess cancer. **Testing a tumour sample, alone, however, only raises suspicion that a mutation might be inherited. Confirmation of a germline inheritance requires testing a blood sample.**

Why have a Hereditary Cancer Risk Test?

A hereditary cancer risk test screens most of the known cancer-predisposing genes for inherited mutations. **Identifying and confirming that these mutations are inherited can:**

- help patients understand how their cancer developed,



- can help point to specific treatments,



- can help focus the search for the same mutation in other unaffected family members and determine whether they have an elevated risk,



- can help unaffected family members at increased risk decide on cancer prevention, cancer screening, early detection or treatment strategies.



How is a Hereditary Cancer Risk Test Done?

It's your choice to have a Hereditary Cancer Risk test. There are many types of cancer gene tests available that test either a tumour or blood sample or both. A Hereditary Cancer Risk test is designed specifically to determine inherited cancer risk and is performed on a blood sample. If you decide to have the test, your healthcare provider will discuss the type of test with you.

1. Your treating doctor will explain the purpose, potential benefits, consequences, risks, and cost of the test and ask you to read, understand, and sign a consent form. Your doctor may refer you to a Genetic Counsellor to discuss the test, or you can choose to see a Genetic Counsellor first.



2. You will be provided with a copy of a consent form and a request form to have blood samples taken together with instructions on how to have the blood samples taken.



3. You will be asked to provide two blood samples taken at least 5 minutes apart. You will be asked to confirm that these samples were taken from you.

4. **All hereditary cancer risk testing must be performed only in a pathology laboratory accredited by NATA/RCPA for cancer germline genetic testing.** Your sample will be couriered to the LifeStrands accredited laboratory in Melbourne for testing. The laboratory will process and extract DNA from both samples and each will be given a unique identifier. One of the samples will be tested and the other will be stored. In the event that a causative mutation is identified in one of the cancer-predisposing genes queried by this test, the other sample will be tested to confirm the finding. Confirmatory testing will add another two weeks to the test timeline and is particularly important as it informs testing of other family members.



5. If a germline mutation is identified that has therapeutic significance, the unconfirmed result will be immediately sent to your doctor so treatment can commence without delay. Testing of the second sample and confirmation for other family members will then follow.



6. **If both tests agree, the lab will send this confidential information back to your doctor,** in the form of a secure written test report. Your doctor will explain your test results to you. Your doctor may refer you to a Genetic Counsellor to discuss your results.



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ACCREDITED
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NATA
NATIONAL ASSOCIATION
OF TESTING AUTHORITY

RCPA
The Royal College of Pathologists of Australia

What is Genetic Counselling?

All individuals contemplating hereditary cancer risk testing should first undergo pre-test counselling. Genetic counselling is a health care service, provided by qualified professionals, that helps individuals and families understand the process of germline genetic or genomic testing. This invariably involves taking a detailed family history and establishing the pattern of inheritance. **This will help determine whether genetic testing is likely to find a mutation.** Individuals considering undergoing genetic testing will be informed of the associated benefits and potential harms to ensure that they are able to make informed decisions and have an opportunity to discuss the potential implications and consequences with their families prior to and following testing.

How do I Receive Genetic Counselling?

Prior to undergoing testing, you will need to receive pre-test genetic counselling from a qualified health practitioner, who might be a medical doctor (i.e., your GP, surgeon, physician, oncologist, or clinical geneticist) or a genetic counsellor. Who performs this service will depend upon various factors.

- For patients with cancer being tested to identify potential new treatments, it is appropriate for the pre-test counselling to be performed by your treating medical practitioner.
- Cancer patients with a suspicious personal and/or family history suggestive of a cancer predisposition can be seen by a genetic counsellor or clinical geneticist who will create a family tree or pedigree and explore the patterns of inheritance, discuss the potential implications of a result, and manage the testing of other family members if required.

Post-test counselling refers to the follow-up process once the results of the genomic tests are known. If a mutation is found, you will likely be referred by your treating doctor to a genetic counsellor and/or a clinical geneticist.

What are the Possible Results of a Hereditary Cancer Risk Test?

If you have cancer and an inherited mutation is identified, then the immediate action is to determine whether there are any treatments available that target the genetic changes that caused your cancer. Your oncologist will advise you on which treatments are available depending upon the stage of your cancer, prior treatments, and government approval and payment. Sometimes, a promising treatment is not yet available and only accessible via a clinical trial. Your oncologist will be able to advise whether you might be eligible, whether a suitable trial is open, and help organize enrolment. The next action would be to seek an appointment with a genetic counsellor or clinical geneticist to take a detailed family history and facilitate testing of your family members.

If you have cancer and no germline mutations were found, then your cancer is unlikely to have been caused by an inherited mutation. However, the hereditary cancer risk test only tests for genes that are known today to be associated with an increased inherited risk. Since new genes and mutations are being discovered, there is still a small chance that your cancer was inherited but is caused by a currently unknown mutation.

Sometimes, however, it is difficult to determine whether an identified inherited genetic error is harmful or not. This is particularly true for rare errors where there have not yet been enough cases studied to determine their harmfulness. In such cases, your error may be referred to as a "variant of unknown or uncertain significance" (VUS). Depending on the policy of the testing laboratory, they may or may not, report these VUS errors because they are presently clinically non-actionable. However, as more cases are studied it may become clearer whether they are or are not harmful.

If you don't have cancer and no germline mutations were found, then you are unlikely to have an elevated inherited risk of developing cancer. However, this does not mean you are at zero risk because there are other non-inherited causes of cancer (e.g., cigarette smoking). You would, therefore, have the same potential risk of developing cancer as the general population without a family history of inherited cancer.

All laboratories are required to retain samples and genetic data, however different laboratories have different policies relating to re-examining previously tested and reported samples. In general, most diagnostic laboratories only issue test results once based on current information. They usually would require a new test request to test a new sample or to re-examine a previously tested and reported sample.

HEREDITARY CANCER RISK TEST RESULTS – IMPLICATIONS AT A GLANCE

No mutations found (without cancer)

Low risk, like general population.
Lifestyle factors still matter.

No mutations found (with cancer)

Cancer likely not inherited.
Slightly unknown genetic risk.

Mutation identified (with cancer)

Guides treatment. Test family.

Variant of Unknown Significance (VUS)

Unclear harmfulness. Usually not
actionable. Needs research.

How is My Genomic Information Protected?

Your results and genomic information from the test will be stored securely using systems that meet Australian and international privacy and security standards and laboratory guidelines. **Your identifiable genomic information is confidential and will only be shared with your consent, unless required or permitted by law.** Further information on how your information is kept private and secure can be sought from your healthcare provider.

Can My Genomic Information Help Others?

Because we are all part of a genetic pool, information about how mutations contribute to cancer is important for all of us, particularly for the development of new medicines. This information is systematically collected and researched to look for new clues and leads. This information is stored and publicly available, mostly through government-sponsored databases. All submitted genetic data must be de-identified such that the individual cannot be identified or traced.

Your de-identified genetic data may be uploaded to genetic databases. Research laboratories or companies, with an interest in a particular cancer or gene, may explore these databases and re-classify the error we reported. However, since your sample was de-identified the updated results would not be returned to your requesting doctor, you or your family. Your genetic counsellor will be able to advise you on how best to monitor scientific advances.

What Else do I Need to Know?

To help you decide whether to have this test, it is important that you are given information specific to your test and have had the opportunity to have all your questions answered in detail by your healthcare provider.

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