NHS
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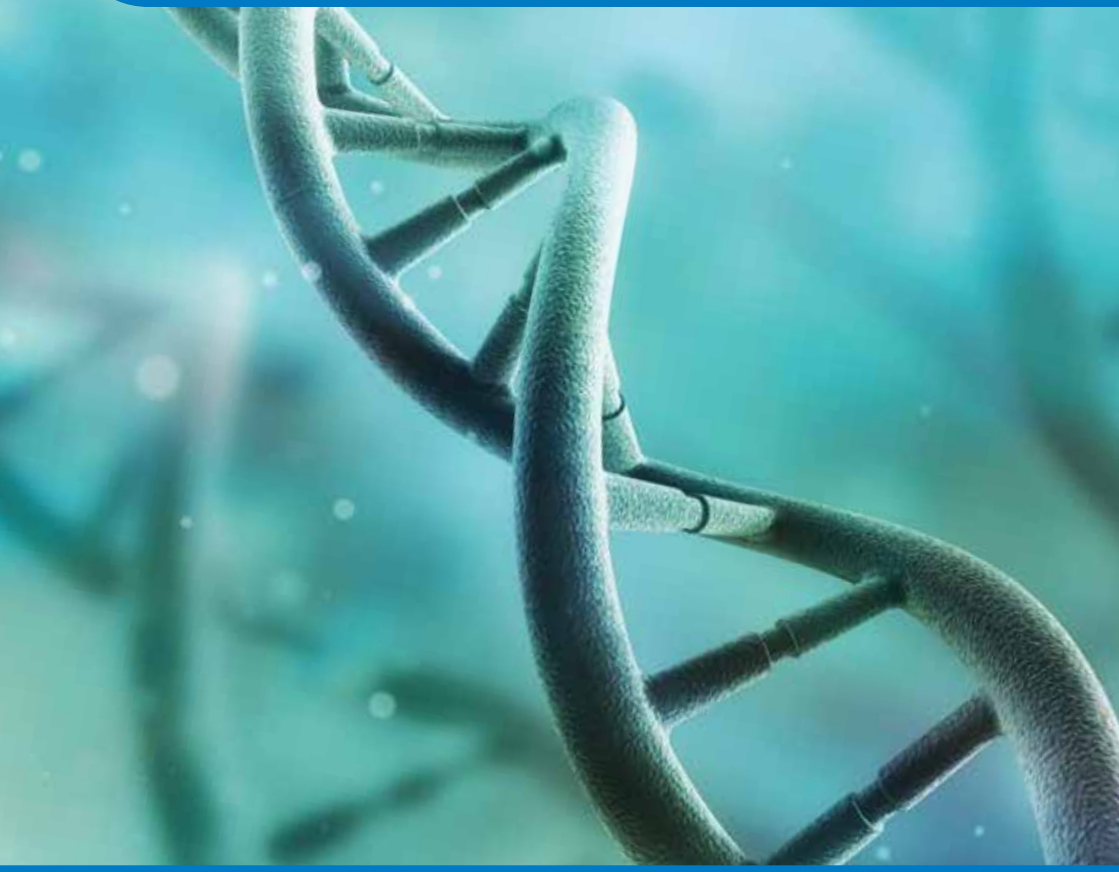
Testing for gene variants in inherited breast, ovarian and prostate cancers

Information for patients, families and carers



We've written this booklet for people who have a personal or family history of breast, ovarian or prostate cancer that could be explained by an inherited factor. We've designed this booklet to be used alongside your clinical genetics appointment, where we will discuss genetic testing, cancer screening, and family communication. We hope it will help to answer some of your questions, but please ask if you would like more information.

Background

Research has shown that people who inherit variants in certain genes (known as BRCA1, BRCA2 and PALB2) have an increased lifetime risk of breast, ovarian, prostate and other cancers.

Several thousand different variants in these genes have been identified so far and each variant may have a subtly different effect on a person's risk of developing cancer. The variants may also increase the risk of other cancers to a lesser extent but our knowledge about these and what risk you might be at is still evolving.

There are other gene variants which are also linked to an increased risk of cancer. These include variants in the TP53 gene (linked to very young onset breast cancers in rare cases) and the CHEK2 and ATM genes (linked to generally lower risks).

How common is cancer?

In the UK, around one in every two people will develop a cancer of some sort in their lifetime. Around one in seven women will develop a breast cancer in their lifetime, and around one in six men will develop a prostate cancer in their lifetime. Around one in 50 women will develop ovarian cancer in their lifetime. Most cancers occur over the age of 50 years, and most are not strongly influenced by variants in the BRCA1, BRCA2 or PALB2 genes.

How do I know if I have inherited a cancer risk variant in the BRCA1, BRCA2 or PALB2 genes?

Genetic factors play a part in most cancers, but inherited factors usually only play a small part. Around five to 10 out of every 100 people with breast, prostate or ovarian cancers will have inherited a variant in one of the BRCA1, BRCA2 or PALB2 genes. It is more likely in people who have close relatives with a history of these cancers, and if the age of onset of these cancers was relatively young (under the age of 50 years for example). Because of this, we will ask you for a detailed family history, as this can show the likelihood of you having one of these variants. In some cases, you may already know that one of these variants has been identified in your family.

What are these genes for?

BRCA1, BRCA2 and PALB2 genes help to prevent cells growing and dividing too rapidly, or in an uncontrolled way. If a variant in one of these genes affects the function of the gene, it can change this control mechanism and increase the chance of developing breast, ovarian or prostate cancer. If you inherit one of these gene variants, you may be more likely to develop one of these cancers than the average person, and it may be more likely to develop at a relatively young age.

How are the gene variants inherited?

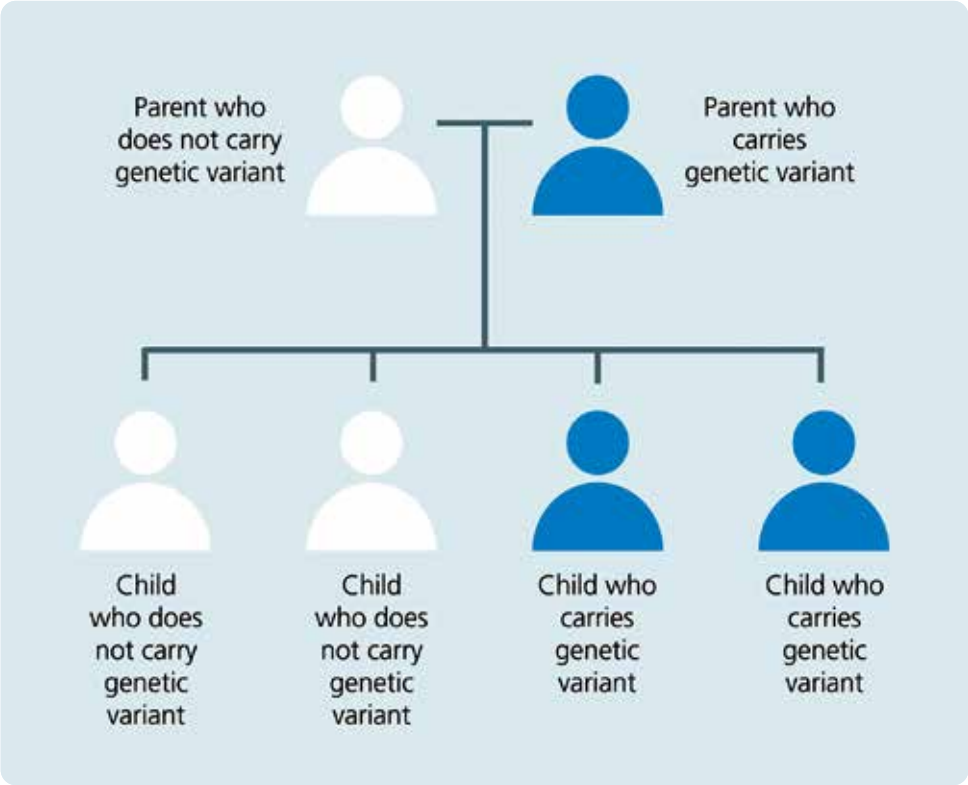
We all have two copies of (most of) our genes, because we inherit one copy from our mother and the other from our father. This means we have two copies of the BRCA1 gene, two copies of the BRCA2 gene and two copies of the PALB2 gene. When someone has biological children they randomly pass on one copy from each pair. If a person has a variant in one copy of the BRCA1, BRCA2 or PALB2 gene, then each of their children will have a 50% (one in two) chance of inheriting it from them.

Sometimes people think that because the genes are associated with (predominantly) female cancers, that they are passed down the female line. This is not the case. You are just as likely to inherit a variant from your father as from your mother.

Not everyone who has a variant will necessarily develop cancer. For example, if your father has a variant but has not developed cancer himself, he may still have passed on that variant to you.

If you don't inherit a variant found in your family, then you can't pass it on to your children. The gene does not skip a generation.

Each child of someone with a variant in the BRCA1, BRCA2 or PALB2 gene has a 50% (or one in two) chance of inheriting the gene variant.



How do I find out if I have a variant in BRCA1, BRCA2 or PALB2?

When we are looking for an inherited variant in a gene, we will usually start with someone in your family who has had breast, ovarian or prostate cancer. We might ask them or another family member to have a blood test so that our laboratory team can test for gene variants. These genes are large (long stretches of DNA) and there are thousands of different variants so the laboratory team will need to go through the genetic code very carefully to check for variants. This can take several months.

If we find a variant that clearly affects the function of the BRCA1, BRCA2 or PALB2 gene, this can explain your family history of cancer. Even if we do not find a variant in one of these genes, this does not rule out a variant in another gene. In most cases of inherited variants, it is the BRCA1, BRCA2 and PALB2 genes that are affected, but there are also many other possible gene variants (we each have approximately 20,000 gene pairs).

What are genetic variants of uncertain significance (VUS)?

Sometimes we find a variant in the gene but it is not clear whether it affects the function of the gene. Not all variants are linked to disease, even in the BRCA1, BRCA2 and PALB2 genes. If we do not know whether the variant affects the gene, it is known as a 'variant of uncertain significance', or VUS. A VUS may turn out to be harmless or we may find that it is linked with cancer.

We may be able to do further investigations to determine whether a VUS is a risk factor in your family, but sometimes we have to wait for the results of testing in lots of other families before we can be certain. If we are not certain, we cannot use it to predict the chance of cancer developing in other family members.

What if a relative with breast, ovarian or prostate cancer is not available for testing? Can I be tested even if I have never had cancer?

It's always possible to do a blood test, but the results may be difficult to interpret in this situation. If you have not had cancer and your blood test does not find a gene variant, we won't be able to tell whether the difference is because:

- you have not inherited the gene variant that is present in your family, or
- the test has not been able to find the variant that is present in your family (for example if the cancers in your family are linked to another gene variant)

In this situation, it is therefore difficult to know how to interpret a result where no variants have been identified.

How many stages are there in the testing process?

1. The first stage is known as 'diagnostic testing'. We test for variants in a person who has had cancer (this could be you or a family member).

2. The second stage is known as a 'predictive genetic test'. If the diagnostic testing has shown that there is a particular variant in your family, other family members can have a test to see if they also have the variant.

Does everyone who inherits a BRCA1, BRCA2 or PALB2 variant develop cancer?

No. These variants do not cause cancer, but they increase the chances of developing cancer. Many other factors such as lifestyle, random factors and other genetic factors play a role in whether a cancer will develop. These factors are likely to interact in a complex fashion and we cannot yet test for these other factors.

It is also important to remember that the chance of developing cancer is **not** the same as the chance of dying from cancer. Even if cancer develops, there is a chance that it will be treated successfully.

What are the risks of developing cancer linked to BRCA1, BRCA2 or PALB2 variants?

The tables below show the average risks of developing cancers according to variants within a specific gene.

BRCA1 gene variant lifetime chance of developing cancer:

	Female with BRCA1 variant	Male with BRCA1 variant	Chance in the general population
Breast cancer	60 to 90%	No known increase in risk	12.5% (female) 0.5% (male)
Ovarian cancer	40 to 60%	Men do not have ovaries	1 to 2% (female)
Prostate cancer	Women do not have a prostate gland	15 to 17%	17%

BRCA2 gene variant lifetime chance of developing cancer:

	Female with BRCA2 variant	Male with BRCA2 variant	Chance in the general population
Breast cancer	45 to 85%	5 to 10%	12.5% (female) 0.5% (male)
Ovarian cancer	10 to 30%	Men do not have ovaries	1 to 2% (female)
Prostate cancer	Women do not have a prostate gland	20 to 30%	17%

PALB2 gene variant lifetime chance of developing cancer:

	Female with PALB2 variant	Male with PALB2 variant	Chance in the general population
Breast cancer	40 to 60%	1%	12.5% (female) 0.5% (male)
Ovarian cancer	1 to 5%	Men do not have ovaries	1 to 2% (female)
Prostate cancer	Women do not have a prostate gland	No known increase in risk	17%

Things to think about before having a genetic test

Knowing your chance of developing cancer may help you with decisions about your life and allow you to make choices to manage your risks. Some people would rather know whether they have inherited the high cancer risk than live with uncertainty. Others feel that knowing they carry a gene variant but not knowing if and when it will cause cancer is not helpful.

It is important to know that there is no method of cancer detection or prevention that is completely effective. Some people expect the test to tell them whether or when you will develop cancer, but it cannot do this.

If a predictive genetic test shows that you have not inherited the variant, your chance of developing cancer is less than if you have inherited the variant. However, it is not zero. You may still need to have additional screening. Sometimes people are disappointed that the result is less clear-cut than they had expected.

If a predictive genetic test shows that you have not inherited the variant, it also means that you haven't inherited a known high risk factor for cancer. In this situation, you cannot have passed the variant on to your children (or future children).

What happens next if I have inherited a high risk variant?

We will discuss screening and other options with you. For example:

Breast awareness

Notice and report any changes in your breasts. Regular breast examination is not a reliable way of picking cancers up early. Instead, you should be aware of changes in your breasts. The normal shape and feel of your breasts may change with your menstrual cycle, but ask your GP about changes that do not feel normal for you, and last for longer than a month or so.

Mammography

A mammogram is an x-ray of the breast. All women in the UK aged 50 and over (or sometimes aged 47 and over) are offered a mammogram every three years through the NHS National Breast Screening Programme.

There is no routine mammography screening for men. If you are at increased risk from your family history, you may be offered earlier mammograms at age 40 and over, or sometimes even earlier.

Magnetic resonance imaging (MRI)

MRI is a method of screening that is offered to women at high genetic risk aged 30 and over, alongside mammography. The advantage of MRI screening is that it does not use radiation (as x-rays do).

Ultrasound scan of the breasts

If you have a lump in one of your breasts, we may use an ultrasound scan to examine the lump. We do not usually use ultrasound scans for screening if your breasts seem normal.

Risk-reducing breast surgery (risk-reducing mastectomy)

This is an operation to surgically remove healthy breast tissue to reduce the chance of breast cancer developing. The reduction in risk depends on how widespread the surgery is but it is not possible to remove every breast cell. This is a major operation and can have significant complications, so it requires careful consideration. If you have a high genetic risk of breast cancer and wish to explore this possibility, we can refer you to a specialist breast surgeon or plastic surgeon to discuss which type of surgery might suit your body shape and age best.

Why doesn't everyone have regular mammograms at a young age?

The cancer detection rate through mammograms is lower in younger women because their breasts are denser than those of postmenopausal women. Mammograms are x-rays, and too many x-rays can increase a person's risk of cancer. This is why mammograms are not usually offered regularly before the age of 40.

Can I have screening for ovarian cancer?

In the past, ultrasound scans of the ovaries and a blood marker (CA125) were used to screen for ovarian cancer, but these did not reliably detect cancer at an early, treatable stage. These screens are still being investigated as research studies, but they are not available on the NHS.

Risk-reducing surgery to remove both ovaries and fallopian tubes (risk-reducing bilateral salpingo-oophorectomy or RRBSO)

The ovaries (and fallopian tubes) can be removed by an operation to reduce the risk of ovarian and fallopian tube cancer. Unfortunately, there is still a small chance of a cancer of the peritoneum (which can't be surgically removed), which is estimated to be between 2 to 5% in a lifetime. This is why the operation is called risk-reducing rather than risk-avoiding.

If you have not yet gone through the menopause, having your ovaries removed will start this immediately. Depending on your age, and whether or not you have had breast cancer in the past, you might be offered hormone replacement therapy (HRT) to replace the hormones that your ovaries would have produced.

This surgery is not usually offered before the age of 40 (because there are health risks associated with a very early menopause). It will also prevent you having any more biological children, so this is something to take into consideration before you have the surgery. Researchers are currently looking at whether earlier removal of the fallopian tubes will help prevent later ovarian cancer.

Does the contraceptive pill affect my chances of cancer?

Taking the contraceptive pill for several years slightly increases the risk of breast cancer, but the risk goes back down to an average level approximately five years after you stop taking it. Taking the contraceptive pill slightly decreases the risk of ovarian cancer. Ovarian surgery reduces the risk much more significantly. Talk to your GP about what type of contraception might be best for you.

Does hormone replacement therapy (HRT) affect my chances of cancer?

Hormone replacement therapy (HRT) is a treatment that relieves the symptoms of the menopause. In the general population, HRT use after the menopause (average age 51 years) increases the chance of breast cancer slightly. This risk appears to be greater the longer HRT is used. We do not know how this risk interacts with the risk from a BRCA1, BRCA2 or PALB2 gene variant. You may want to talk to your doctor about what the risks might be and whether to take HRT. If you have inherited a variant of BRCA1, BRCA2 and PALB2 and you have gone through early menopause after RRBSO (see above), you may be offered HRT until the average age of the menopause (age 51). In this situation, HRT does not appear to increase the breast cancer risk, and may help to protect against bone thinning and heart disease.

Are men offered screening for breast cancer?

No, but men who have a BRCA2 gene variant should be aware of the natural shape and feel of their breasts (chest) and tell their GP if they notice any changes.

Are men offered screening for prostate cancer?

Men who have a BRCA2 gene variant can request a yearly PSA (prostate specific antigen) blood test through their GP from the age of 40. However, we do not know whether this screening will help to reduce deaths from prostate cancer.

This is not recommended for men with BRCA1 or PALB2 gene variants because the risk of prostate cancer is unclear.

Most men with early prostate cancer don't have any signs or symptoms. Contact your GP if you have difficulty starting to urinate or emptying your bladder, or need to urinate more often, especially at night.

Lifestyle factors and cancer risks

Smoking

Smoking carries a risk of heart disease, lung cancer, head and neck cancer and pancreatic cancer. It increases the risk of serious complications after surgery, and women considering risk-reducing mastectomy may not be able to have this surgery unless they stop smoking. Smoking may increase breast cancer risk in people with the BRCA2 gene variant.

Diet and weight

Obesity increases the risk of many common cancers, including breast cancer. If your BMI (body mass index) is above 30 then weight reduction will be important alongside a healthy balanced diet and regular physical activity. Risk-reducing surgery is more difficult in someone who is obese. Your GP can refer you to weight reduction and activity programmes.

Pregnancy and breastfeeding

For all women, pregnancy increases the risk of breast cancer but the risks go back down to average levels within a year after delivery. It is possible that breastfeeding may reduce the ovarian cancer risk in women with the BRCA1 gene variant.

Alcohol intake

Alcohol increases the risk of breast cancer in the general population. As with the contraceptive pill and HRT (see above), this is a small additional risk on top of the risk from BRCA1, BRCA2 or PALB2 gene variants.

Other cancers

In some families with BRCA1, BRCA2 and PALB2 gene variants, there are other cancers that are seen more frequently. For example, pancreatic cancer and melanoma are seen more frequently than average in BRCA2 variant families. However, the overall lifetime risk is still quite small. There are no other screening interventions we currently recommend for other cancers.

Things to consider before having a BRCA1, BRCA2 or PALB2 predictive test

In countries where health care is based on a person's ability to pay insurance, people may worry that genetic testing will affect their insurance prospects. In the UK, a voluntary code of practice with the insurance industry means that insurance companies will not ask you to have a genetic test, or for the results of that test, if it is a 'predictive test'. Visit **www.gov.uk/government/publications/code-on-genetic-testing-and-insurance** for more information. You can also talk to your doctor about how the information will be kept in your medical records, so that it is not released to insurance companies. Although the code of conduct prohibits the use of genetic test results in deciding your premium, insurance companies can use a family history of cancer to do so, and you must answer such questions to the best of your knowledge.

Anger, shock, anxiety, worry about your health, worry or guilt about possibly passing the gene variant on to children are all common reactions after finding you have a BRCA1, BRCA2 or PALB2 gene variant. Some people may feel guilty about not inheriting the variant, especially when close family members do. Please use your genetic clinic appointment to consider if and when a variant test would be right for you.

Do I need to tell family members my result?

Your test result may mean that other family members now also need to be told about their risk of cancer. We will talk to you about when and how to contact your family members. We may be able to provide general information about the gene variant in the family that you can share with them. This may be a difficult topic to discuss with your family and it may also bring up unexpected information. For example, someone may disclose that a family member is adopted.

Can I take part in any research?

Yes, there are often different types of research studies that you may be able to take part in. We can discuss this with you in the genetic clinic. Whether you take part in research studies or not will not affect the clinical care you receive. Please be aware that research studies are designed to deliver generalised findings to improve future care and so they may not benefit you directly.

The team involved in your care are:

Consultant: .....

Telephone: .....

Genetic counsellor: .....

Telephone: .....

Please contact us on 023 8120 6170 if you have any other questions.

Useful links

www.uhs.nhs.uk/departments/genetics

Notes

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