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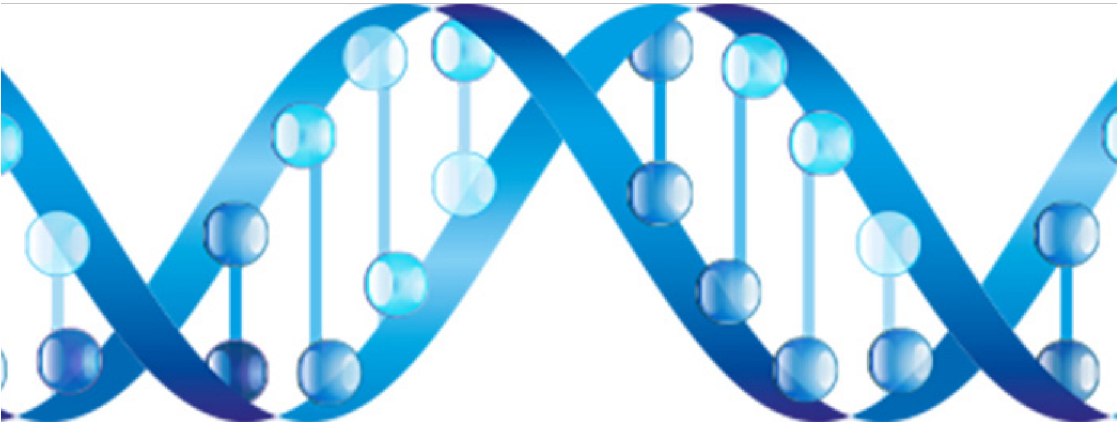
GENETIC TESTING FOR INHERITED BREAST AND OVARIAN CANCER



DIAGNOSTIC GENETIC TESTING

GENETIC TESTING FOR INHERITED BREAST AND OVARIAN CANCER

This booklet has been written for people who have a personal or family history of breast or ovarian cancer that might be explained by an inherited factor, and for those who are considering having genetic testing.

ARE BREAST AND OVARIAN CANCERS INHERITED?

It is uncommon for breast and ovarian cancer to be caused by an inherited pathogenic (disease-causing) change in a high-risk cancer gene. In the UK, around 1 in 7 females* will be diagnosed with breast cancer in their lifetime, whilst around 1 in 50 will receive an ovarian cancer diagnosis. Around 5-10% of these cases are thought to be linked to an inherited gene change, whilst the other 90-95% are thought to be caused by a combination of age, lifestyle, environmental exposures, and low risk genetic factors. Currently, we can offer testing in our clinics for several breast and ovarian cancer predisposition genes; the most appropriate genes to test will be determined by your personal and family history of cancer.

* refers to biological sex assigned at birth

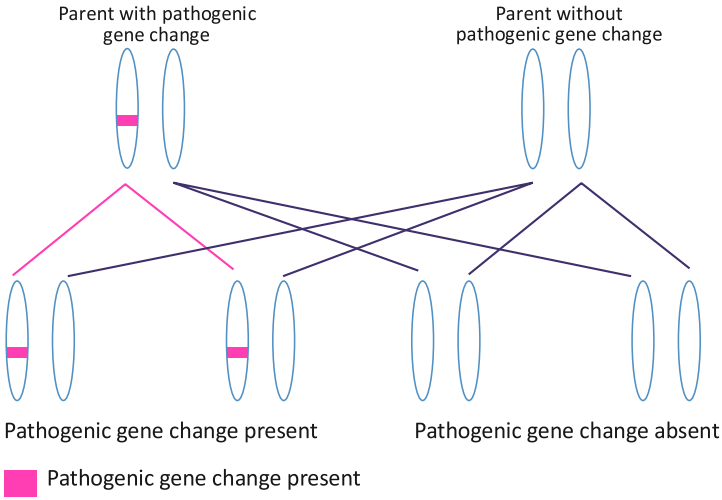
WHAT ARE CANCER PREDISPOSITION GENES?

We each have several genes which normally help to protect us from developing cancer. These are known as **cancer predisposition genes**. The most well-known are BRCA1 and BRCA2, but we now know of, and can test many others. Some individuals inherit a change within one of their two copies of a certain cancer predisposition gene that prevent it from working properly. This can therefore increase their risks of developing certain cancers compared to the risks for the general population. The associated risks vary depending on which cancer predisposition gene is affected. Cancers caused by hereditary gene changes are also more likely to occur at a younger age than cancers in the general population.

HOW ARE THESE GENES INHERITED?

All of our genes come in pairs; we inherit one of each pair from our mother and the other from our father. When we have children, we randomly pass on one of each gene pair. If an individual has a pathogenic change in one copy of a cancer predisposition gene, each of their children (male or female) has a 50% (1 in 2) chance of inheriting it. If they do not inherit the copy with the pathogenic gene change, they cannot pass it on to their own children. For most cancer predisposition genes, having a pathogenic change in one of the two copies is associated with increased cancer risks. This is known as '**autosomal dominant inheritance**'.

AUTOSOMAL DOMINANT INHERITANCE



CAN I HAVE A TEST TO SEE IF THE CANCERS IN MY FAMILY ARE DUE TO A PATHOGENIC CHANGE IN IN A CANCER PREDISPOSITION GENE?

Possibly. You may be offered a blood test that examines a number of genes that are known to be associated with increased risks of developing breast and/or ovarian cancer. However, since the majority of cancers are not due to an inherited cause, pathogenic changes in cancer predisposition genes will only be found in a small proportion of those with cancer.

Genetic testing is usually only offered to individuals who meet specific testing criteria. This commonly includes those with certain tumour types, a strong family history of certain cancers, usually across multiple generations, and/or those where individuals have been diagnosed at a young age.

We usually start by obtaining a blood sample from an individual who has been affected by cancer. The sample is then tested to see if any pathogenic changes are present within the genes of interest. This is called **diagnostic testing**. Finding a pathogenic gene change in a relative who has had cancer is the key to developing a genetic test for other family members. Testing for other family members is then known as **predictive testing**. We know that at present we cannot find all the causes of inherited cancer. Some families may have a genetic predisposition to developing cancer but due to limits in our scientific knowledge the laboratory may not yet be able to identify it. There are continuous efforts being made to better understand the genetics of inherited cancers.

WHAT ARE GENETIC VARIANTS OF UNKNOWN SIGNIFICANCE?

Occasionally we find a change in a gene of interest and we are not sure of its significance. These are called variants of uncertain significance (VUS). There are many genetic differences between individuals, and it is often unclear whether these VUS's are just part of normal human variation, or whether they are disease-causing. If we are uncertain whether a gene change found is the cause of the cancers in your family, we will not be able to offer genetic testing for this in unaffected relatives, as we would also not know what results of this mean for them. We may however offer testing to family members who have been affected by cancer to try and gather more information to help determine whether the VUS is the explanation for your family history of cancer.

IF A RELATIVE AFFECTED BY CANCER IS NOT AVAILABLE FOR TESTING, CAN I BE TESTED EVEN IF I HAVE NEVER HAD CANCER?

We generally prefer to test a person who has had cancer as this gives us the greatest chance of finding a disease-causing gene change if there is one present. If there are no living relatives who have had cancer, certain family history eligibility criteria must be met before genetic testing can be offered. This will be reviewed on an individual basis by a genetic health professional.

DOES EVERYONE WHO HAS A PATHOGENIC CHANGE IN A CANCER PREDISPOSITION GENE DEVELOP CANCER?

Not everyone with a pathogenic change in a cancer predisposition gene will develop cancer. We do not yet understand why some people develop cancer and others do not. We know that lifestyle and other genetic factors play a role. It is important that all women are breast health aware, and check their breasts regularly. We strongly encourage participation in the NHS breast screening programme from the age of 50. The NI-based charity 'Action Cancer' offer earlier access to screening for those aged 40-49.

WHICH GENES WILL I BE OFFERED TESTING FOR?

Your healthcare professional will decide which is the most appropriate genetic test. If you are being offered testing in a mainstream clinic (e.g. by your surgeon or oncologist), and there is an additional family history of other cancers, you may be referred to the Genetic Medicine team to ensure that you are getting the best test available for you. The two most common genes associated with hereditary breast and ovarian cancer are known as BRCA1 and BRCA2. However, many other less common cancer predisposition genes are now known, and often those having diagnostic genetic testing for breast or ovarian cancer will be offered a **multigene panel**. These panels look at several relevant genes in a single blood test (such as PALB2, ATM, BRIP1, CHEK2, PTEN, RAD51C, RAD51D, TP53, STK11, PMS2).

HOW WILL I RECIEVE MY GENETIC TESTING RESULT?

The healthcare professional who arranged the test for you will inform you of your result when it is available. If you were offered testing by a mainstream clinician (e.g. surgeon or oncologist), and a pathogenic change is found in any of the genes that were tested, you will be offered an appointment with clinical genetics. During this, will receive the most up-to-date information available at that time, tailored to their personal and family history of cancer.

WHAT ARE THE CANCER RISKS ASSOCIATED WITH PATHOGENIC CHANGES IN CANCER PREDISPOSITION GENES?

This depends on which gene the pathogenic change has been found in. For some breast and ovarian cancer predisposition genes, the associated risks vary significantly when family history is considered. Your genetic health professional may give an individualised risk figure which takes into account your family history and individual circumstances.

For some of the rarer breast and ovarian cancer predisposition genes, not enough is known about the associated cancer risks to provide accurate risk estimations. Researchers are continuously working on better characterising these.

The table below shows the approximate lifetime cancer risks for individuals with a pathogenic change in their BRCA1 gene *

	BRCA1 Carriers (Female)	BRCA1 Carriers (Male)	General Population
Breast Cancer	72%	0.4%	14% (female) Rare (male)
Ovarian Cancer	44%	-	2% (female)
Prostate Cancer	-	12-17%	12% (male)

The table below shows the increased risk of cancer over a lifetime for an individual who carries a pathogenic change in their BRCA2 gene *

	BRCA2 Carriers (Female)	BRCA2 Carriers (Male)	General Population
Breast Cancer	69%	4%	14% (female) Rare (male)
Ovarian Cancer	17%	-	2% (female)
Prostate Cancer	-	27-41%	12% (male)

* It is important to note that the figures quoted refer to the risk over an individual's lifetime, up to age 80-85. The risks of developing the associated cancers increase

with age. (Risk figures from '**UK Cancer Genetics Group**' *https://www.ukcgg.org* July 2023)

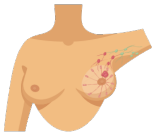
I HAVE CANCER, COULD THE RESULTS OF GENETIC TESTING AFFECT MY TREATMENT?

If you have breast or ovarian cancer, the results of genetic testing can help your oncology team in making the best choices for your current and future cancer management. Knowing whether or not you have a pathogenic change in a high-risk cancer predisposition gene may affect which chemotherapy drugs or surgery would be most suitable for you.

IF A PATHOGENIC GENE CHANGE IS FOUND, WHAT ARE MY OPTIONS?

It is important to note that genetic testing can also reveal information about your risk of developing other cancers. For individuals known to have increased risk of developing certain cancers, additional screening may be available to detect the early signs of cancer, or there may be risk-reducing surgical options. These will vary greatly depending on which of the genes the pathogenic change is found.

The following options are relevant to those where a pathogenic gene change is found in **BRCA1** or **BRCA2**:

Cancer type	Screening Options	Surgical Options
 Breast Cancer	Annual breast MRI scans from 25 years Annual mammograms from 40 years	Risk reducing mastectomy (removal of breast tissue with or without reconstruction)
 Ovarian Cancer	Screening has not proven to be effective	Removal of ovaries and fallopian tubes- when childbearing is complete and no earlier than 35-40 (BRCA1) and 40-45 (BRCA2). Your genetic professional may discuss participation in the PROTECTOR study (more information can be found at the link below)*
 Prostate Cancer	Men with a pathogenic gene change in **BRCA2** can be offered annual prostate specific antigen (PSA) blood tests from 40 years. These can be requested from your GP on an annual basis.	N/A

* http://protector.org.uk/information-for-participants/

For the other genes included in the multigene panel test, screening is determined on an individual basis according to current screening guidance. Specific management options will be discussed with you in your results appointment. If a

pathogenic gene change is found, your genetic health professional will refer you to the relevant healthcare specialists to discuss screening and surgical options.

WHAT DOES IT MEAN IF NO PATHOGENIC CHANGES ARE FOUND?

If you have a cancer diagnosis and diagnostic testing does not find any pathogenic gene changes, this reduces the chance that your caner is due to an underlying genetic cause in the genes that we offered testing for. There is still a small chance that there is a pathogenic change in a gene that has not yet been associated with breast/ovarian cancer, and therefore was not included in the test. Sometimes when there is a considerable cancer family history but no identifiable pathogenic gene change, increased screening recommendations may be given for yourself and some relatives to reflect this.

WILL GENETIC TESTING IMPACT MY INSURANCE PROSPECTS ?

Insurance companies may consider an individual's personal medical history, and their family history (including cancer) when setting up policies and calculating premiums. Medical history will need to be disclosed for some types of insurance. These commonly include life cover, critical illness insurance, and income protection insurance. Detailed information about genetic testing and insurance can be found in the 'Code on Genetic Testing and Insurance' at:
https://www.abi.org.uk/globalassets/files/publications/public/genetics/code-on-genetic-testing-and-insurance-final.pdf

ARE THERE ANY OTHER IMPLICATIONS OF GENETIC TESTING?

The results of genetic testing may provide information about your relatives' risk of developing cancer. If you are found to have a pathogenic gene change, there is a chance that other people in the family have also inherited this.

Some people experience a range of emotions when they are told they have a pathogenic change in a cancer predisposition gene. They may feel angry, shocked, anxious, or guilty about possibly passing the pathogenic gene change on to their children. They may also feel guilty if they have not inherited the pathogenic change when other close family members have. Others feel relieved to have an explanation for their cancer, and are empowered to make medical and health decisions to lower their risks of developing another cancer in the future.

SHARING TEST RESULTS WITH RELATIVES

Whether your results are positive or negative, it is important to share them with relatives. If a pathogenic gene change is found, sharing those results can help family members identify their own risks sooner and take appropriate action. Sharing negative test results is also helpful because then your relatives will know that they do not need testing. Sharing genetic testing results with relatives can be difficult for many people. Your genetic counsellor can provide advice and support with this, along with written information on how your relatives can seek a referral to our service (if a pathogenic gene change is found in you). It is important to note that for the majority of cancer predisposition genes we do not offer predictive testing to children- those who wish to be tested between the ages of 18 and the minimum screening age will be assessed on an individual basis.

ARE THERE ANY RELEVANT SUPPORT GROUPS FOR PEOPLE WITH PATHOGENIC CHANGES IN CANCER PREDISPOSITION GENES?

Action cancer is a Northern Ireland-based charity provide free breast screening to women aged 40-49 and 70+ who fall outside the NHS screening age range, and health checks to men or women aged 16+
https://actioncancer.org

BRCA link NI is a Northern Ireland based organisation helping people with Hereditary Breast and Ovarian Cancer access information and support. They organise group meetings and formal events with guest speakers.
http://brcani.co.uk/about.html

National Hereditary Breast Cancer Helpline provide support and information to those concerned about their hereditary cancer risk through their website and phone helpline.
https://www.breastcancergenetics.co.uk

Together in Surgical Menopause is a UK-based patient-led resource for those experiencing surgical menopause, for example due to risk-reducing removal of the ovaries.
http://www.surgicalmenopause.co.uk/index.html

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Family reference number:

The health professionals involved in your care are:

Genetic Counsellor: _____

T: _____

Consultant: _____

T: _____

If you have any feedback or comments regarding the contents of this leaflet, we would be pleased to receive them at genetic.medicine@belfasttrust.hscni.net ; If your relative has given you this leaflet and you would like to discuss testing for yourself, please ask your GP to refer you to your local genetics service. There is also the option to self-refer via our website (linked below). However, **this should only be done if there is a confirmed gene change in the family**. Those who self-refer to our service based on cancer family history alone will be declined. https://belfasttrust.hscni.net/service/laboratory-services/clinical-genetics/how-to-make-a-referral-to-clinical-genetics/.

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