

Information for *PALB2* Carriers and their families

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Introduction

1. What does it mean to have a *PALB2* alteration?

This information booklet was put together to provide answers to some of the questions people have when they receive the news that they carry a *PALB2* gene alteration. Healthcare professionals working in Cancer Genetics have met many people who have inherited cancer predisposition conditions and we can share our experience to some extent. We can provide information and make referrals to other healthcare professionals. We can tell you that other people in your situation have had similar feelings and anxieties, but we do not truly know what it is like for you and how it may affect your life.

Many people have questions that, for the time being, cannot be answered fully because we are still studying the *PALB2* gene and its impact. One of the challenges that people with *PALB2* alterations face is coping with the uncertainty of what the future holds, both for you and your family. You may be asked to make life-changing decisions about cancer surveillance and risk-reducing surgery without the benefit of all the facts you would like. This may be difficult and could cause you to feel quite anxious, frustrated or even angry at times. It may take you some time to feel that you have absorbed enough information to feel confident about your decisions.

There is an extra set of challenges for people with a *PALB2* alteration - the risks for your relatives. If you are the first person in the family to have been diagnosed with the *PALB2* alteration, you will have to find a way to share this information with your family. Even if you are not the first person in the family to be tested, there may be family pressures to face. Will relationships be affected if one person has a *PALB2* alteration and their relative does not? What about starting a new relationship - when do you tell someone and what do you say? What if you have young children or are planning a family?

We hope that this guide will be useful in providing you with some of the information you need and help you to think about questions you may wish to discuss with your family and the genetics department. We realise that the guide contains some detailed information, which may be new to you. If you have any difficulties in understanding the information, or have any queries about this, please contact your genetics professional. If you have any comments about the guide, do let us know. We would like to make this booklet as useful and accessible as we can to support you and your relatives.

2. Background information about the *PALB2* gene.

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Is breast cancer inherited?

Generally speaking, cancer is not an inherited illness. Breast cancer is common, in women, affecting about 1 in 8 women and rare in men. It is not unusual to have a relative who has been affected by breast cancer. Most breast cancer occurs sporadically or 'out of the blue'. However, we know that harmful alterations in certain genes are the underlying cause for about 5-10% (5 to 10 in 100) of breast cancers. There are several genes (BRCA1, BRCA2, PALB2, TP53, CDH1 and PTEN) that, if mutated, can cause a high risk of breast cancer. *PALB2* is one of these genes. Approximately 1 in 700 people carry a *PALB2* alteration. Research to identify new genes that also contribute to a high risk of cancer or modify the risk associated with a high-risk gene alteration is ongoing.

What is the *PALB2* gene?

Genes are pieces of the DNA code that we inherit from our parents. We have two copies of each gene; one copy is inherited from our mother and one from our father. We have about 20,000 genes, each with a specific function that helps our bodies grow and function normally. The *PALB2* gene is a tumour suppressor gene, and it works to protect against cancer by correcting damage that can occur in the DNA during cell division. If an individual has an alteration in the *PALB2* gene, they have a greatly increased risk of developing breast cancer and slightly higher risk of other cancers.

The *PALB2* gene alteration does not cause cancer to occur on its own. The individual is at greater risk of developing cancer because their cells' ability to repair DNA damage may be impaired by the gene alteration. It is the build-up of DNA damage which causes a cell to change into a cancerous cell. We also do not yet understand why alterations in the *PALB2* genes primarily give a high risk of breast cancer rather than other types of cancer.

Cancer risks associated with *PALB2* alterations vary according to your family history of cancer. This may be because other genes modify the effects of the *PALB2* genes and therefore affect a person's cancer risk. At the moment, your estimated cancer risk will be mostly based on the gene alteration that you carry and your personal and family history of cancer. In the future we may be able to use information from other genetic tests, such as polygenic risk scores (PRS), to clarify cancer risk. PRSs look at the cumulative effect of multiple gene alterations, which individually only influence cancer risk very slightly, but when combined can have a more significant effect on this risk.

There are several factors which will affect your own personal cancer risk. However, we don't fully understand how these factors interact to influence your overall risk.

- Age
- Gender
- Gene alteration
- Family history of cancer
- Previous cancer diagnoses
- Previous surgery (e.g., if you have had your womb/ovaries removed)
- Diet and lifestyle

PALB2 Cancer Risks

What are the cancer risks associated with *PALB2* gene alteration?

An individual's lifetime cancer risk is determined by both the presence of a *PALB2* alteration and their family cancer history. For example, if you have a strong family history of breast cancer, your breast cancer risk is at the higher end of the risk range.

Cancer	Population risk by age 80	PALB2 risk by age 50	PALB2 risk by age 80
Female breast cancer	12-15%	13-21%	44-63%
Male breast cancer	0.1%	Less than 1%	Around 1%
Pancreatic cancer (men & women)	1.5%	Less than 1%	2-3%
Ovarian cancer	1.5%-2%	Less than 1%	Around 5%

3. Breast Cancer

Risk factors

Aside from the *PALB2* gene alteration, your risk of breast cancer is influenced by your family history of breast cancer and by other factors. Some factors you can change and others you cannot. Some risk factors increase your risk significantly and some only a little bit. Your genetics team can help estimate your lifetime risk of breast cancer using all this information.

Factors that increase your risk of breast cancer

In addition to the inherited, environmental and lifestyle factors that increase an individual's risk of cancer in general, the following may specifically increase your risk of breast cancer:

- Being a woman
- Early menstrual periods and late menopause
- First pregnancy after 30 or never having a full-term pregnancy
- Never breast feeding
- Having dense breasts
- Personal history of breast cancer or certain non-cancerous breast diseases.
- Previous treatment using radiation therapy
- Taking hormones: Taking HRT for an extended period after natural menopause, or taking the Pill for more than 5 years

What are the symptoms of breast cancer?

If you have any concerning symptoms, you should report these to your GP even if you have recently had a mammogram or breast MRI. Your GP can refer you on an urgent cancer assessment pathway - this is the fastest way to get an assessment of any possible breast cancer symptom. This advice applies to both men and women.

Discuss any of the following symptoms with your GP:

- A new lump or area of thickened tissue in either breast.
- A change in size or shape of either or both breasts
- Discharge of fluid from either or both nipples
- A Lump or swelling in either or both armpits.
- Dimpling on the skin of either of your breasts

- A rash on or around either or both nipples
- A change in the appearance of either or both nipples Please note breast pain is not usually a symptom of breast cancer.

Managing your breast cancer risk

Breast Awareness

We recommend all women practice breast awareness. This means being aware of changes in the breast and feeling the breast with the flat of the hand in a systematic way, once a month, 5 - 10 days after the menstrual period (if applicable). It is also important to take time to look at the breasts in different positions. If there are any changes at all, women should inform their doctor. All women should practice this from their early twenties.

Breast surveillance

Women who have a *PALB2* alteration have an increased lifetime risk of breast cancer. Therefore, breast surveillance by breast MRI and/or mammograms are recommended. The surveillance aims to pick up breast cancer at an early stage when it is easier to treat and more likely to be cured. Breast surveillance does not change the breast cancer risk. Breast surveillance also cannot prevent the cancer occurring. Breast surveillance is provided through the NHS breast surveillance service.

Breast Surveillance Guidelines for Women with a *PALB2* alteration

Type of Surveillance	Age (years) at which breast surveillance recommended	How often
Breast MRI	25-40	once a year
MRI + Mammogram	40-50	once a year (both)
Mammogram only	50+	once a year

At what age does breast surveillance start?

All women who carry a *PALB2* alteration should receive annual breast surveillance with MRI from age 30. Some women who carry a *PALB2* alteration, whose risk of developing breast cancer is greater than 8% from age 25-30 will be referred earlier to start surveillance, but not before age 25. For women aged 25-30 who carry a *PALB2* alteration, their genetics team can calculate their risk of young onset breast cancer using Canrisk (www.canrisk.org) that considers their genetic diagnosis and personal and

family history information. Their genetics team will then make surveillance recommendations accordingly.

At what age does breast surveillance finish?

Once referred for surveillance you can continue with annual breast surveillance for your whole life. After age 70 you will not receive automatic invitations, but you can request annual surveillance. If you have had breast cancer you can be referred to the surveillance programme once you are discharged from breast cancer, follow up. Women who choose risk-reducing breast surgery of both breasts will not require breast surveillance.

Chemoprevention

Chemoprevention describes drugs that are used to reduce the risk of cancer developing. This is different from chemotherapy which describes drugs that are used in the treatment of cancer and the term is confusing as drugs used in chemoprevention are not the same as those used in chemotherapy. In general chemoprevention drugs block or alter the effects of oestrogen. Guidance from NICE (National Institute of Clinical Excellence) published in March 2017 recommends that chemoprevention should be considered in women at increased risk of breast cancer based on their family history. We do not have data to know if chemoprevention is appropriate for *PALB2* carriers.

Risk reducing surgery.

If your lifetime risk is estimated to be greater than 30%, based on your genetic test results, your family history, and your other breast cancer risk factors you may wish to consider risk reducing mastectomy with reconstruction. Risk-reducing breast surgery is the removal of the breast tissue to try to prevent the development of cancer. There are various types of operation, but - in general - as much as possible of the breast tissue is removed. Some operations leave the nipple behind and some remove this and reconstruct a new nipple. An implant may be inserted to recreate the shape of the breast. Not all the breast tissue can ever be removed and - therefore - there is always some breast tissue remaining which may be at risk of developing breast cancer. The remaining risk is about 5% or less. Unlike breast surveillance this option greatly reduces the chance you will develop breast cancer in the future. We do not yet know if risk reducing breast surgery helps you to live longer than breast surveillance with early treatment for any breast cancer that may develop.

4. Pancreatic cancer

Both men and women who have a *PALB2* alteration may have a slightly increased risk of pancreatic cancer. If you have a *PALB2* alteration it is important to not smoke, cut down on alcohol consumption and maintain a healthy weight as these are also risk factors for pancreatic cancer.

What are risk factors for pancreatic cancer?

- Age - risk increases with age - mainly affects people between 50 and 80.
- Being very overweight/obese
- Smoking
- Having a history of health conditions such as diabetes, chronic pancreatitis, or stomach ulcers
- Hereditary factors for example: a *PALB2* alteration

What are the symptoms of pancreatic cancer?

It is important to be aware of pancreatic cancer symptoms and discuss any concerns with your GP. The first noticeable symptoms of pancreatic cancer are often:

- pain in the back or stomach area - which may come and go at first and is often worse when lying down or after eating.
- unexpected weight loss
- yellowing of the skin and whites of the eyes (jaundice) - Jaundice may also cause dark yellow or orange urine, pale-coloured poo, and itchy skin.

Other possible symptoms of pancreatic cancer include:

- feeling sick and being sick
- change in bowel habit (diarrhoea or constipation)
- fever and shivering
- indigestion
- blood clots

It is important to remember that these symptoms can be caused by many different conditions and are not usually the result of cancer.

Is pancreatic cancer surveillance available?

Currently there is no proven test or group of tests that can reliably diagnose pancreatic cancer at an early stage. Therefore, no routine surveillance for pancreatic cancer is currently available. There is a research study called EUROPAC looking into pancreatic cancer surveillance and if you have a *PALB2* alteration and a family history of pancreatic cancer you could be eligible to join this study. Please see Section 19 for details.

5. Ovarian Cancer

Women who have a *PALB2* alteration may have a slightly increased risk of developing ovarian cancers during their lifetime. More research is needed to better understand the ovarian cancer risk in *PALB2* families. Your risk will be assessed based on your family history and age, as well as the presence of a *PALB2* alteration.

What are the symptoms of ovarian cancer?

It is important to be aware of ovarian cancer symptoms and discuss them with your GP. Ovarian cancer symptoms can be vague/ nonspecific. Research shows that any of the following three symptoms, if they occur on most days may suggest ovarian cancer:

- persistent pelvic and abdominal pain
- increased abdominal size or persistent bloating (not bloating that comes and goes)
- difficulty eating and feeling full quickly.

Occasionally, women may also experience other symptoms, such as urinary symptoms, a change in bowel habit, extreme fatigue, or back pain, on their own or at the same time as those listed above. If you regularly experience any of these symptoms and they are not normal for you, see your GP. There is further information available on the NHS website. Please see Section 19 for details.

What is my risk compared with other women?

On average, women have about a 1.5-2% chance of developing ovarian cancer in their lifetime. Women with a close relative affected with ovarian cancer have a slightly increased risk of around 4-5%. Women who have a *PALB2* alteration may have an increased risk of ovarian cancer. Their risk of developing ovarian before age 50 is less than 1% and their risk by age 80 is around 4-5%. If you have a family history of ovarian cancer and a *PALB2* alteration your lifetime risk may be closer to 10%. At this level of risk, you may wish to consider risk reducing surgery. Some women who have a *PALB2* alteration, but no family history, may also consider risk reducing ovarian surgery after age 50.

How can I manage my risk of ovarian cancer?

Currently there is no proven form of surveillance for ovarian cancer. Large studies have evaluated the use of trans-vaginal ultrasound scans and CA125 blood tests for ovarian

surveillance. The results showed that surveillance for ovarian cancer does not help to identify ovarian cancers at an early enough stage to make a difference to treatment or prognosis.

Using oral contraceptives (birth control pills) decreases the risk of developing ovarian cancer for average risk women and BRCA mutation carriers, especially among women who use them for several years. Women who used oral contraceptives for 5 or more years have about a 50% lower risk of developing ovarian cancer compared with women who never used oral contraceptives. We do not have any data on effects on PALB2 carriers, but we would expect to see a similar effect.

Birth control pills do have some serious risks and side effects such as slightly increasing breast cancer risk. Women considering taking these drugs for any reason should first discuss the possible risks and benefits with their doctor.

Women who have a lifetime risk of ovarian cancer that is >10% (greater than a 1 in 10 risk) may consider having their ovaries and fallopian tubes removed. This procedure is called a risk-reducing bilateral salpingo-oophorectomy (BSO).

What is a risk-reducing bilateral salpingo-oophorectomy (BSO)?

A risk-reducing bilateral salpingo-oophorectomy (BSO, Bilateral (both sides) salpingo- (fallopian tube), oophor- (ovaries), ectomy (excision of)) is the surgical removal of a woman's ovaries and fallopian tubes before an ovarian cancer has occurred. This surgery is carried out to reduce the risk of developing ovarian or fallopian tube cancer. It can be done by keyhole surgery for many women, which significantly reduces the recovery period.

6. Other cancer risks

There is not enough information yet to determine if a *PALB2* alteration causes an increased risk of other types of cancer. Your risk for other types of cancer will be based on your family history of cancer. It is important to stay in touch with your genetics team over the years to make sure you have up to date information. And it is essential to go back to your genetics team anytime there is a new diagnosis of cancer in your family in case this changes your cancer surveillance advice.

7. *PALB2* cancer risks for men

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Men who have a *PALB2* alteration have a raised risk of breast cancer compared to men who do not have a *PALB2* alteration. Approximately 1 man in 100 men (1%) with a *PALB2* alteration will develop breast cancer. There is no breast cancer surveillance for men. Men should be breast aware and report any changes in their breast tissue to their GP. Men, like women have a slightly increased risk of pancreatic cancer and should follow the same advice as outlined above.

There is insufficient evidence to suggest that a *PALB2* alteration causes an increased risk of prostate cancer therefore a man's risk of prostate cancer would be based solely on his family history of that type of cancer.

Men are also at slightly increased risk of pancreatic cancer. Please refer to this section of the booklet for more details.

8. New cancer treatment options for people with a *PALB2* alteration

If you need cancer treatment your oncology team will need to know you have a *PALB2* alteration as it may change the treatment you are offered. Treatment choices may include established chemotherapy drugs such as platinum based chemotherapies or may include entry into clinical trials looking at new treatments such as PARP inhibitors. For this reason, it is important to discuss the offer of genetic testing for the familial *PALB2* alteration to anyone in your family who has a history of a *PALB2* related cancer.

Your oncologist may discuss a clinical trial with you. These trials help to establish the best treatment for a particular type of cancer and sometimes will include the use of new drugs. If you are seeking information on cancer trials, you should discuss this with your oncology team. Please see Section 19 for details.

Sharing information with your family

9. Genetic testing for your relatives

Who needs to know that *PALB2* alteration has been diagnosed in my family?

During your genetic appointment, the doctor or the genetic counsellor will go through your family tree with you to identify who is at risk of inheriting the familial *PALB2* alteration. Your close relatives (brothers, sisters, and your children) will have a 50% chance of inheriting the *PALB2* alteration. In many families it will be possible

to predict if the gene alteration came down through your mother's or your father's family, because of the family history of cancer. However, the only way to prove this is to test family members to see who has the altered gene. Only your relatives from that side of the family will be at risk of having the *PALB2* alteration. This process of testing can also help to guide which distant relatives like cousins, may benefit from a referral to genetics to discuss their own choices.

What do I tell people?

You will have received quite a lot of information about the *PALB2* alteration, your risks, and your options. It can be daunting to know how to share all this information with someone else. Many people worry that they will be asked questions and they will not know the answers. Your genetics unit will not approach your relatives about your result, so usually it is you who would provide this initial information about the presence of an altered gene to the family. The genetics clinician can provide you with a 'to whom it may concern' letter for you to share with your relative(s) which contains all the required information so that they can ask for a referral from their GP to their local genetics' unit.

Why do other people in my family need this information?

Genetic information is different from most medical information an individual receives because it is not only relevant to the individual but also to their family members. Genetic information can provide an explanation as to why someone has a particular health problem, but it can also predict future poor health or the risk of having a child affected with a particular genetic problem. If someone is aware that they have an increased risk of developing cancer, they have the chance to make choices about genetic testing, cancer surveillance or preventative surgery. They may also decide to make changes to their lifestyle to help decrease their risk of developing cancer, and they may wish to consider the family planning implications and insurance issues. Knowing about the risk gives your relatives a chance to take action to reduce their risk of getting cancer or help ensure that cancer is detected at an early stage so it can be treated more effectively.

It is normal practice for genetics services to share information about a specific gene alteration in the care of different family members, however, your other medical information would not be shared without your explicit consent. Sharing information does not mean family members have to choose a particular course of action. It allows

them to make an informed decision about their choices and access the right information and support whilst they do this.

When should I share this information?

There is probably no 'right' time to tell people. Sometimes families are aware of the testing process and are waiting to hear the results. Other people choose to wait until they know their results before they mention it to anyone else. There will be a variety of factors that affect your decision to share this news. For example, you may need time to get used to the information first, or someone may have been bereaved recently and you may feel it is better to wait a bit. Sometimes people are too young to be told everything or maybe you are waiting until you have the chance to see someone in person rather than telling them over the telephone or by mail.

Breast surveillance for a woman who has not had cancer starts sometime between age 25-30. The exact age is determined by the level of risk for that person. For example someone with more risk factors will start at a younger age. As this is based on individual risk, the starting age may be different for two people in the same family. Anyone in the family who has been affected with cancer should be told as soon as possible, because their doctors may need this information to make appropriate treatment decisions.

How can I avoid upsetting my relative?

Many people are concerned that sharing this information will cause their relative to feel anxious or guilty and may feel responsible for causing this upset. Remember it is natural and normal for people to feel upset. Although it will be difficult to share 'bad' news, but it is important information for your family. It can help if you think about it in a positive light. If your family has this information, they will be in a better position to make choices which could reduce their risk of cancer or ensure it is detected as early as possible. It is important to remember that if someone has the *PALB2* alteration it is nobody's fault - we cannot control which genes were passed on to our children. It is also important to remember that if someone has a *PALB2* alteration, they have always had it since the moment they were conceived, so what is different now is that we can identify it and give people options to manage their risk.

Where can I get help with telling my family?

The genetics team can help you to identify who needs to be informed in your family and provide you with a 'to whom it may concern' letter. It can be a burden to have this responsibility. Perhaps there is someone else within your family that you could share the information with and who could then help by taking on some of the responsibility of telling other people within the family. In some families, we see the information being passed on to one generation and it is then passed down within family units. The genetics clinician can discuss strategies for sharing information with you to make it as easy as possible.

10. Who is at risk of having the *PALB2* alteration in my family?

If you have a *PALB2* alteration, your close relatives have a 50/50 risk of having the altered gene. The gene alteration is highly likely to have been present in your family for many generations. It is only that we are now able to identify who carries the *PALB2* alteration. You would almost certainly have inherited the alteration from either your mother or your father. It is extremely rare for a person to carry a *PALB2* alteration which has not been inherited from one of their parents.

Your brothers and sisters:

Your brothers and sisters each have a 50/50 risk of having the gene alteration. Each person will need to have genetic testing to determine if they have it or not. You cannot predict if someone has the altered gene based on their brothers' or sisters' genetic test results or if people look alike in the family.

Your children:

Your children (or future children) each have a 50/50 risk of having the gene alteration. We do not offer predictive testing to children because surveillance or risk-reducing treatment is not generally needed or available for children. Once they are 18 or older, each of your children could choose to have genetic testing to find out if they have inherited the *PALB2* gene alteration or not.

If you have more than one child, each of your children will have a 50/50 risk of carrying the gene alteration. This is regardless of the way that they look, their personality traits, or whether their siblings carry the gene alteration. Sometimes, a parent with *PALB2* alteration will not have passed the gene alteration onto any of their children. In other cases, all or some of their children will have inherited the

gene alteration. Even if your children have inherited the gene alteration, they may not ever develop a cancer.

Cancer treatments, surveillance and risk-reducing strategies do improve over time. Therefore, the options available to your children when they are adults may be different to those options which have been available to you.

Your extended family:

The altered gene would either have come down through your mother's or your father's family. So, if you inherited the gene alteration from your mother, for example, then only your aunts, uncles, and cousins on your mother's side of the family are at risk of having the *PALB2* alteration.

Does the *PALB2* alteration skip a generation?

The altered gene does **not** skip a generation. Not all individuals with a *PALB2* alteration will develop cancer. For this reason, it may look as if the alteration has skipped but, it was present in the previous generation.

Is the gene alteration only important if you are a woman?

When thinking about who is at risk of having the alteration in the family, it does not matter if you are a man or a woman. Both men and women have the *PALB2* gene.

How do I know who to tell about the gene?

When you have your appointment in the genetics clinic, the doctor or genetic counsellor will go through your family tree with you and explain who is at risk of having the gene alteration and who is not at risk. We can provide you with a letter that provides information about the gene alteration for you to share with your at-risk relatives; they can then decide if they want to have a genetics appointment to find out more information.

Some people will need to consider how to tell any future partners about their *PALB2* alteration. This is important to consider and there may be no right time. When talking to your partner about the risk of passing on the gene alteration to future children, they may have questions of their own which you are unable to answer. In this case, it might be helpful to request a genetics appointment and invite your

partner to attend, so that they can ask questions of their own. You could also encourage them to read this guide.

What does 'dominant inheritance' mean?

You may have heard the term 'dominant inheritance' at your genetics appointment when the doctor or the genetic counsellor was describing how the gene alteration is passed down within the family. When we understand how a gene is passed down in a family, we can then determine who is at risk of having the altered gene in the family.

We have about 20,000 genes. These genes are the instructions that our bodies need to develop and function normally. All genes come in pairs; we get one copy from our mother and the matching copy from our father.

A dominant condition is one where a person only needs one of the two genes to have an alteration, to be affected. Having one altered (mutated) copy of the *PALB2* gene is enough for someone to have the increased risk of developing cancer, even though the other copy of the gene, which they inherited from their other parent, works normally.

Therefore, we know that if a person carries a *PALB2* alteration there is a 1 in 2 or 50% chance they will pass the altered copy of the gene to their offspring: hence the 50% risk for children. We can also work out the risk for extended family members by looking at how they are related to the person in the family who has the *PALB2* alteration.

11. Predictive genetic testing

What does predictive genetic testing mean?

This term refers to a genetic test that is offered to someone who is healthy (for example, has not had a diagnosis of a cancer which is associated with a *PALB2* alteration). It is sometimes also called "pre-symptomatic testing". The purpose of the test is to determine if the person has inherited the gene alteration that has already been identified in one of their close relatives. It is called a predictive test

because if the person has the altered gene, it means they have an increased risk of developing these cancers over their lifetime. Not everyone who has a *PALB2* alteration goes on to develop cancer, but the risk is increased.

Who can have predictive testing?

Close relatives of an individual with a *PALB2* alteration can ask to be referred to their local genetics service by their GP to access genetic counselling. The genetic counselling process involves talking about *PALB2* risks and how they can be managed as well as genetic testing. Your genetics clinician will go through the family tree to show you who in your family is at risk of having the *PALB2* alteration. We do not offer predictive genetic testing to children because this is an adult-onset disorder, so cancer surveillance or interventions are not necessary for children.

What happens when someone is referred for genetic testing?

If someone is coming for a predictive genetic test, they may have one or two appointments to discuss the issues around testing, depending on their age and their understanding of the genetic information.

The first step for the genetics department is to confirm that there is a gene alteration in the family and obtain a copy of the relative's genetic report. If the report is not available, then predictive genetic testing may not be possible. At their first appointment, the doctor or counsellor will explain what the altered gene is, how it is inherited and their risk of having inherited it, the associated cancer risks, and their cancer surveillance or risk-reducing options. They will also discuss whether the individual wants to have a test at this point in their life, who they have for support and who they have told about the test. They will also discuss how a result could impact on the individual's life and their relationships within the family. Exploring an individual's motivations for having a genetic test are a core part of a genetic counselling session and enables the genetics clinician to support you through the process in a holistic way. A letter summarising the consultation is sent to the individual after the clinic appointment. If they decide to have the test, results are available within a few weeks and are usually given by letter. If someone is found to carry the gene alteration, they will be invited to attend another clinic appointment. Individuals are welcome to bring a friend or relative with them to the appointment for support.

What if someone does not want genetic testing?

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Not everyone who is at risk of having a *PALB2* alteration wishes to have a predictive genetic test. Even if someone does not want genetic testing, it is still useful to talk to them in the genetics clinic. We can explain the options and give them a chance to ask any questions.

Does predictive genetic testing have a negative impact on insurance?

Sometimes people worry that if they have a genetic test, they will have problems taking out life insurance. There is an agreed code of practice amongst insurance companies that that results of predictive testing for high-risk cancer genes will not be used by ABI insurers to determine premiums or eligibility for life insurance. Further information can be found on their website. Please see Section 19 for details.

Planning to emigrate?

If you are planning to emigrate to a new country, it would be good to check with that country's relevant office to determine if having a predictive genetic test could impact either your emigration application or your ability to obtain health insurance and/or health care provision before undertaking genetic testing.

12. Talking to children and young people about the *PALB2* alteration

Many parents find the prospect of talking to their children about the presence of a *PALB2* alteration in the family difficult and distressing. Studies show that parents' first instinct is to protect their children and they find it difficult to know what and when they should tell their children. Parents are often dealing with their own concerns about their health and future wellbeing and can feel a sense of guilt that their children may also be at risk.

What helps children and young people?

In most cases, children cope better when the family is more willing to discuss what is happening to different family members. Talking to children helps them feel valued and respected and helps them cope better than when they are left feeling confused and unsure how or what to ask.

Children get information from many places including school, television, and friends. They are likely to already have some knowledge about cancer and possibly about

hereditary cancer. By talking to them, you can help them sort out what is accurate and what is inaccurate and clarify things they are not sure about.

Children will probably be most worried about their parent developing cancer, so they will need reassurance and reminders that having a *PALB2* alteration does not always result in cancer. However, knowing you carry the gene alteration means that you can have regular tests to ensure that if a cancer arises, it can be detected very early on, so it is easier to treat.

When is a good time to tell your children?

There is no 'right' age but try not to keep secrets. Children and young people place great emphasis on trust and honesty from parents. Children often observe changes in their parent's behaviour and may try asking questions or may be waiting for you to discuss what is happening. Watch for any changes in your child's behaviour; it may indicate that they are worried or concerned about what they have observed or overheard.

Research suggests that by the age of eight years, children learn not to ask difficult questions unless their parent(s) gives them permission because they fear upsetting their parent(s). Therefore, you may have to prompt your child, and let them know you are willing to talk with them about the *PALB2* alteration. This applies to older children too.

What information do you tell children?

Try to respond to children's questions using language appropriate to their age. Providing small amounts of information gradually is likely to help children understand and cope best. Check on the question being asked so that you find out what your child wants to know.

Explain and provide the name '*PALB2* alteration' - children cope better because knowing the name allows them to discuss it with you, and this knowledge gives them a sense of control. Parents can place a positive emphasis on the importance of knowing about a diagnosis of a *PALB2* alteration because it means there are improved surveillance and perhaps treatment options. By the time children become adults, there may also be even better treatments available, which you can explain to your child.

Communication tips

- Children and young people prefer informal discussion often while doing other things together, for example, driving, cooking, or gardening.
- Check their understanding because children worry about upsetting their parents and so may not always ask.
- Talking about the *PALB2* alteration is an ongoing discussion rather than a one-off conversation. Like adults, children probably need information given to them more than once. They may need time to digest information and then want to come back and discuss it with you.
- Discuss information young people find on the internet or in newspapers.
- Discuss emotions; provide reassurance they are not alone.
- Explain parents' behaviour if they are anxious or upset.
- Being with peers, for example cousins, in similar circumstances might be helpful.
- Support and guide decision-making, especially with young people, who usually like to make their own decisions but with advice from parents.
- If you do not know the answer, explain some questions do not have answers or that you will try to find out for your child.
- Agree appropriate times to discuss the *PALB2* alteration and cancer if your child asks questions at difficult or awkward moments.

What are children likely to know about genes and inheritance?

8-11 years: They have a very basic understanding of heredity and that they share characteristics with parents. They may talk about genes but not fully understand what they are. Often children of this age cope with simple explanations in response to their questions and are not easily upset, although you may have to reassure them that having the *PALB2* alteration is not the same as having cancer. Children and young people can easily confuse this, so it often needs repeating throughout development into adulthood.

12-14 years: Children are beginning to develop more insight about hereditary. They will begin to recognise that you having the gene alteration may have implications for them but will usually cope well if you explain there is only a 50% chance of them having the *PALB2* alteration.

15-17 years: Children recognise the risks to their parent, themselves and often their future children and can begin to consider genetic testing. By this age, young people will be learning about hereditary diseases in school curricula.

Most children are quite pragmatic in response to genetic risk in families affected by inherited genetic conditions. Children and young people are often focused on developing friendships, school, and their personal interests, so do not dwell on the risk.

What helps parents talk to their children?

It has been observed that the following points have helped parents talk to their children:

- Younger children do not have the experience to recognise and anticipate the fuller implications so there is a gradual realisation.
- Not feeling under pressure to talk before an impending event, for example, a school science lesson.
- Talking was a relief for parents and ultimately easier than keeping the secret.
- Parents can be the role models for young people - giving them insight into how to cope with the risk.
- Recognising siblings may all have different needs; trying to find out what each understands at different times in their development.
- Ensuring children and young people understand a positive genetic test is not a cancer diagnosis - some get quite confused about this.
- Belief in a child's right to know.
- Support of other family members, friends, and health professionals.
- Attendance at support groups gave focus to regular discussion with children and young people, with parents discussing where they were going and what had been discussed when they returned.

Preparing to talk to your children.

It might be worth considering the following benefits and drawbacks in preparing to talk to your child but try to take naturally occurring opportunities where possible.

Benefits

- Makes the family closer.
- Provides support for children.
- Gives insight and helps them realise that parents being upset about the *PALB2* alteration is not down to them or their behaviour; it is 'no fault' of theirs
- Gives children confidence to talk to close friends.
- Children and young people feel valued by parent(s)
- Allows discussion of the *PALB2* alteration and cancer risk without centralising it to life.
- A shared reality and understanding helps children and young people cope.
- Reduces risk of children getting inaccurate information from elsewhere.

Drawbacks

- It can be emotionally taxing dealing with questions.
- Children and young people can remind you about the *PALB2* alteration when you do not want to be reminded.
- Questions can arise at difficult or awkward moments - explain when it is appropriate to discuss it.
- Children may want to talk to peers, but networks can be limited.
- Can affect schoolwork for a short time (but so can worrying about what is happening in their family if there is secrecy)

[Alison Metcalfe & Gill Plumridge (June 2010 Version 2)]

Miscellaneous

13. Family planning

If you are found to have a *PALB2* alteration before you have your family, you may have some questions about risk for your future children and you may wish to know if anything can be done to minimise this risk. Anyone with an inherited condition has a risk of passing it on to their children. The risk depends on the specific genetic condition, as there are several ways an inherited condition can be passed on in a family.

If you have a *PALB2* alteration, it is a dominant condition. Therefore, there is a 50/50 or one in two chance that each of your children could inherit the gene alteration. This risk is the same for each pregnancy. The concept of dominant inheritance is explained in more detail in an earlier section of this booklet. Everyone who has a genetic condition can

choose from a variety of family planning options and each option has pros and cons. It is a highly personal decision for you and your partner, and many factors may influence your choice. There is no right or wrong decision; you should make the choice that best suits your circumstances, feelings, and beliefs. In summary the options are:

1. Have your children without any intervention. Each child would have a 50% chance of inheriting the gene alteration and if they inherited the alteration, they would be at an increased risk of developing cancer as an adult.
2. Pre-implantation genetic diagnosis (PGD) - some couples choose this option to avoid passing the *PALB2* alteration to their offspring and avoid prenatal testing and possibly termination. There is no guarantee this technique will result in a successful pregnancy and funding for it on the NHS may not be available to all couples (for further information, see section 14).
3. Adoption - some couples choose to adopt a baby to avoid the risk of passing the gene alteration to the next generation.
4. Egg or sperm donation - by using donor eggs (if the mother carries the gene alteration) or donor sperm (if the father carries the gene alteration) couples can avoid passing the *PALB2* alteration to the next generation.
5. Prenatal testing - some couples may choose to become pregnant naturally and have a test during the pregnancy to see if the baby has inherited the gene alteration. The couple would plan to continue the pregnancy if the baby has not inherited the alteration. However, if the baby has inherited the alteration, they would choose to end the pregnancy.
6. Some couples decide not to have a family at all because they are very concerned by the risk of passing on the gene alteration.

If anyone expresses an interest in finding out more about any of the other options, we can help make referrals or direct people to the appropriate services. We are happy to talk about these options in more detail at a genetic counselling appointment if you would find that helpful.

Pre-conceptual assessment

It is useful to review your partner's family history of cancer to see if they might have a pattern of cancer that is suggestive of a *PALB2* alteration. If a couple both carry a *PALB2*

alteration, there is a 1 in 4 chance that their children would inherit two PALB2 alterations. This results in a condition called Fanconi anaemia which causes childhood onset bone marrow failure, physical abnormalities, organ defects and childhood cancers. Fortunately, this a very rare condition because very few people have a PALB2 alteration but before you start your family it is useful to look at the history of any medical problem in both families.

14. Pre-implantation Genetic Diagnosis (PGD)

We are often asked about PGD. Below is a brief overview of PGD, as well as websites for more detailed information

What is it?

PGD is a technique used to select embryos that have not inherited the gene alteration which causes the genetic illness or cancer predisposition in a family.

Why would people consider having PGD?

Some couples wish to ensure that they avoid passing on a gene alteration to their children. They want to be confident that their children will not be affected with the genetic illness or cancer predisposition (although it is important to point out that a risk of cancer would still be present in a child without the genetic alteration, just like for everyone else). Alternatives to PGD could include prenatal testing and termination of affected pregnancies, using donor sperm or eggs, adoption or deciding not to have children.

How is it done?

PGD is carried out in conjunction with an IVF (in vitro fertilisation) procedure. The egg and sperm cells are collected from each parent and the embryos are created outside the woman's body. The embryos are then tested for the genetic alteration in the family. Only embryos that have not inherited the genetic alteration are selected to be implanted.

Who can have PGD?

If an individual has a specific gene alteration that is known to cause a predisposition to cancer, they may be able to have PGD. If there is a strong family history of cancer, but no gene alterations have been identified or genetic testing is not possible in your family, then PGD is not an option.

If you have had cancer and stored embryos prior to treatment and your treatment has left you unable to have children naturally, you would need to have an in-depth discussion about the pros and cons of using PGD technology with the PGD team.

Where can I find out more about PGD?

If you are interested in considering this option, please ask your genetics clinician to refer you to a PGD centre. There is one NHS PGD centre in London which offers testing for inherited cancer syndromes. At your first appointment they will discuss all aspects of PGD, including fertility assessment, funding applications, licence applications, time frame, risks, and success rates. It can take many months from the first appointment to starting treatment, so you may wish to ask for an initial consultation long before you want to start your family. Please see section 19 for details.

15. Lifestyle and Diet

Individuals with *PALB2* alterations are recommended to follow the same advice as those in the general population with regards to lifestyle and diet. These measures are known to help reduce the risk of cancer in the general population. It is not known exactly how lifestyle and diet impacts upon cancer risk in people with *PALB2* alterations. Further information about lifestyle advice can be found on the Cancer Research UK website.

- Eat a healthy diet with plenty of fruit and vegetables.
- Eat plenty of fibre.
- Avoid eating too much cured and processed meat.
- Avoid eating too much red meat.
- Take regular exercise.
- Maintain a healthy weight.
- Do not smoke.
- Avoid excessive alcohol.

16. Current studies and trials

Individuals attending the cancer genetics clinic may be offered an opportunity to take part in appropriate research trials. Specific details about research projects that are currently open can be obtained from the genetics team.

Taking part in research

Taking part in research studies is voluntary, and if you prefer not to take part in research that is not a problem at all. We invite everyone we meet in the clinics, who is eligible, to take part in research. If you would prefer that we did not ask you, then please let one of the clinicians know so that we can make a note of your preference. We have many research projects running at one time, and it is likely that you will be invited to take part in several studies. You will be given an information sheet about each study and given as much time as you need to think about whether you would like to take part in the study. You will also be given the opportunity to ask any questions about the research project, including any benefits or disadvantages of taking part. With all research, if you decide to take part, you are free to withdraw at any time, without giving a reason and this would not affect the standard of care you receive.

Confidentiality

If you decide to take part in a research project, any information you give us for the purposes of the study will be treated like all medical information. It will be kept strictly confidential and will be accessible only to the immediate study team. Information is stored on databases adhering to guidelines set out in the Data Protection Act. If specimens (for example, blood or urine) are obtained from you as part of the study, they will be stored using identifying codes that will be known only by the research team. If you decide to withdraw from a study and you would like us to destroy any samples that you have provided for research, we will be happy to do so.

Types of research project

Epidemiological studies: studies looking at the interaction of environmental, lifestyle and genetic factors in the development of cancer.

Surveillance studies: studies looking at new methods of surveillance for cancer.

Psychosocial studies: studies looking at the emotional and societal impact of disease.

Drug trials: studies looking at the use of new drugs for treatment or prevention of cancer.

Tissue bank: the storage of samples in a sample bank for future research

17. Insurance

Insurance implications of genetic testing for individuals who have had cancer.

If you have been diagnosed with cancer and have been offered a genetic test because of your cancer diagnosis, you are having a diagnostic genetic test. This includes cancer diagnoses that occurred in the past, even if treatment has been completed. The

diagnostic genetic test may either be a full test of one or more genes associated with developing cancer (such as testing for several genes that can cause a high risk of breast cancer), or a specific test for a gene alteration that has been identified in your relative.

For Life, Income Protection and Critical Illness insurance policies, insurers can ask for information about your diagnostic genetic test to set the level of cover and cost of your premiums, in the same way as they ask about the rest of your medical history. For example, if you have been diagnosed with breast cancer that is due to a *PALB2* alteration, that genetic information is part of your personal medical history. However, insurers cannot ask you to take a genetic test and can only ask for the results of a genetic test you have already had.

If you are offered a diagnostic genetic test after your insurance policy is in place, then you do not have to disclose that you have had a genetic test or the results of the test. If you are taking out a new insurance policy after you have had a genetic test, you will need to disclose that you have had the test along with the results. Genetic test results do not have to be volunteered for health or travel insurance policies but associated medical conditions such as cancer diagnoses do need to be disclosed.

If close relatives without cancer are taking out a new insurance policy (Life, Income Protection or Critical Illness) they would need to tell the insurance company about both the cancer diagnoses in the family and if any are due to a genetic diagnosis, if they are aware of this information. Relatives without cancer do not have to disclose the results of their own predictive genetic testing to insurance companies, but may choose to do so, particularly if their test result is negative.

Insurance implications of genetic testing for individuals without cancer

If you have not had cancer and have been offered a genetic test because there is a known alteration in the family or because no family members with cancer can be offered a genetic test, you are having a predictive genetic test.

There is an agreed Code of Practice amongst members of the Association for British Insurers (ABI) that information about predictive genetic tests for cancer predisposition gene alterations are not used by insurance companies to determine if a policy is offered, or to determine the cost of the policy. The agreement relates specifically to Life, Income Protection and Critical Illness insurance products only. Health insurance and travel insurance policies are not specifically covered by the agreement, but also do not require disclosure.

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It is important to note that insurance companies will assess risk based on family history information, as they have always done.

If any of your relatives have had cancer due to a cancer predisposition gene alteration, both the cancer diagnoses and the genetic test results are part of your family history information that should be disclosed. You are only required to provide the requested information that you are aware of at the time of taking out a new policy. If a relative has had cancer and/or genetic testing but you were not aware of it when you took out the policy, this will not subsequently be used to alter the policy.

You can choose to disclose your genetic test result. For example, if your test shows you do not have the gene alteration that caused cancer in your relatives this may have a favourable impact on your premiums as it reduces the impact of family history on your risk of cancer. Further information can be found on the ABI website. Please see section 19 for details.

Insurance Implications for those living abroad.

The implications of genetic testing on insurance for those patients living abroad depends on the country of their residence. The rules and regulations regarding this topic can change over time.

In the Republic of Ireland, for example, it has been illegal since 2005 to consider the results of a genetic test, whether positive or negative, in relation to insurance, mortgages or employment. Insurance companies can, however, still ask questions regarding a person's family medical history and it is a legal requirement that the questions be answered truthfully and comprehensively.

It is important for individuals in other countries to ask genetics professionals in their local genetics department about the specific laws regarding genetic testing in their country of residence. Some people may wish to get formal legal advice before going through genetic testing.

18. Blood Donation

Can I still be a blood?

People with inherited predispositions to cancer, such as a *PALB2* alteration, can still be blood donors, subject to the usual conditions set by the blood transfusion service.

19. Organ donation

Can I still be on an organ donor list?

People with inherited predispositions to cancer, such as a *PALB2* alteration, have asked if they can still register to be an organ donor, given that they carry a gene alteration and/or personal history of cancer. The NHS Organ Donation information team provided the following information:

There are only two conditions where organ donation is ruled out completely. A person cannot become an organ or tissue donor if they have been diagnosed with HIV or have, or are suspected of having, Creutzfeldt-Jakob disease (CJD). Cancer is one of the diseases that can be passed from donor to the recipient. However, the risk that this will happen depends to some extent on the type of cancer, the treatment received and the length of time since the disease was diagnosed and treated. Corneas can always be used. At the time that donation is being considered:

- The family would be asked about any history of cancer

- The medical records would be reviewed -A report would be obtained from the GP, although this is not always available pre-transplantation

So, if the potential donor had been confirmed as having a genetic predisposition to cancer this would be reported as part of the assessment process pre-donation and would be included as part of the information provided to the transplant surgeon. A decision will then be made by a healthcare professional, at the time of death, about whether the organs can be used.

How can I register to be an organ donor?

If you do decide to register, please make sure that you have informed your family, both so that they are aware of your wishes and to ensure the information about your genetic status is available for the assessment. People can sign up to the register at their website. Please see section 20 for details.

20. Where can I get more information?

This list of resources is intended to help you find further information or additional sources of support. Some patients may find these websites and charities helpful, but not all information will be relevant to all individuals.

Please consider the source of the material, for example clinical practice in the US may differ to clinical practice in the UK. Responsibility for the content of the information remains with the organisation that publishes it. The hyperlinks worked at the time of publication but may change over time. We will update links when this resource is reviewed.

Genetics

- [PALB2 interest group](#)
- [Genetic Alliance UK](#)
- [Genetics Home Reference \(US\)](#)
- [Predictive genetic testing for PALB2](#)
- [FORCE charity](#)
- [The Centre for Pre-Implantation Genetic Diagnosis](#)

Breast cancer

- [High risk breast screening](#)
- [Breast Cancer Care Now](#)

Ovarian cancer

- [Target Ovarian Cancer](#)
- [NHS website](#)
- [Cancer Research UK](#)
- [American Cancer Society](#)

Pancreatic cancer

- [Pancreatic Cancer UK](#)
- [EUROPAC study](#)

Trials and Research

- [Cancer Research UK](#)
- [Clinical Trials](#)

Insurance

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- [Association of British Insurers \(ABI\)](#)

Organ Donation

- [Organ donation UK](#)

21. Glossary of Terms

Alteration - this term is used through and refers to a harmful change in the PALB2 gene which is associated with increased cancer risk. There are other terms used to describe alterations including a PALB2 mutation, a faulty PALB2 gene, a pathogenic PALB2 variant, a likely pathogenic PALB2 variant. These terms all mean the same.

Mammogram - This is an X-ray picture of the breast. They are used to look for cancers that are too small to see or feel.

MRI Breast - Magnetic resonance imaging (MRI) is a non-invasive medical imaging test with no radiation (no X-rays). It uses magnetism and radio waves to create detailed pictures of the breasts.

Surveillance – It is also referred to as screening and describes tests that are offered to people to detect cancer before symptoms appear.

VUS (Variant of uncertain Significance) this term refers to a change (variation) in a gene that has an unknown effect on a person's health. There is usually not enough information about a VUS to know whether it increases a person's risk of developing a disease, such as cancer. It cannot be used to offer genetic testing to relatives or to clarify future cancer risk. Also called unclassified variant, variant of uncertain significance, and variant of unknown significance.