Genetic testing for women with cancer predisposing genes

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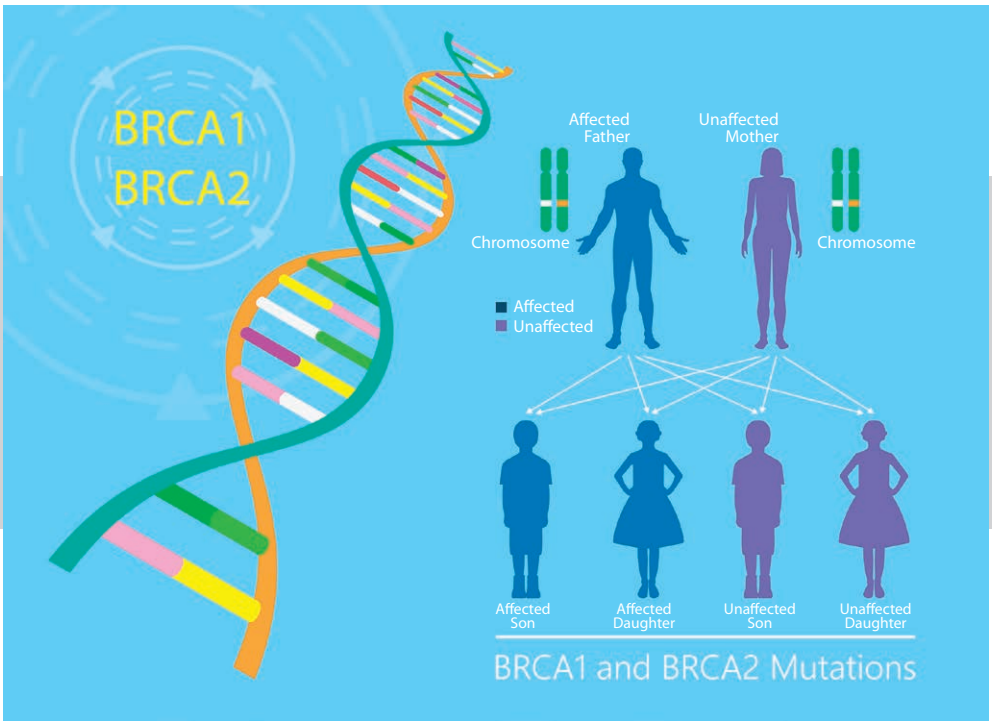
Introduction

Gynaecological cancers are those which affect the womb, ovaries, cervix, vulva or vagina. There are many different types of these cancers. Most occur by chance and are not inherited. A small number are caused by faults in our genetic material, which may be passed down through families.

Our genetic material is made of DNA. DNA is our personal set of instructions on how to build the body. DNA is grouped together into genes. The human body contains approximately 25,000 genes. Half of our genes are inherited from our father and half from our mother. This means that if there is an error in any gene, there is a 50 % or 1 in 2 chance of passing this gene down to your children.



Gene mutations

An error or alteration in a gene is called a gene mutation. The instructions in a gene are like a code. Each gene corresponds to a unique set of instructions.

IMAGINE THE CODE OF A NORMAL GENE IS:

1-2-3-4-5-6-7-8-9-10-11-12-13-14-15-1-2-3-4-5-6-7-8-9-10-11-12-13-1-2-3

There may be an error or 'spelling mistake' leading to a slightly different code:

1-2-3-4-5-6-8-8-9-10-11-12-13-14-15-1-2-3-4-5-6-7-8-9-10-11-12-13-1-2-3

This gene will give slightly different instructions to the cells it controls than a gene with a normal code. This is called a mutation or gene alteration.

Gene mutations (alterations) and cancer risk

Some gene mutations (alterations) increase the risk of developing cancer. Gene mutations can cause 15-20% (up to 1 in 5) of ovarian cancers and 3% (1 in 33) of womb cancers (endometrial cancers). Genes which increase the risk of gynaecological cancers are: BRCA1 and BRCA2, PALB2, RAD51C, RAD51D, BRIP1, MLH1, MSH2, MSH6 and PMS2. Alterations in BRCA1/BRCA2, PALB2, RAD51C, RAD51D and BRIP1 are associated with an increased risk of ovarian cancer.

Alterations in the genes MLH1, MSH2, MSH6 and PMS2 can lead to the development of womb cancer. MLH1, MSH2, MSH6 can also cause ovarian cancer.

To better understand risk, if a person's risk is 10%, this means 1 in 10 people with this alteration would develop this cancer type during their lifetime.

The two genes most associated with ovarian cancer are **BRCA1** and **BRCA2**. For women with a BRCA1 alteration, the risk of developing ovarian cancer is 44%. For women with a BRCA2 alteration, this risk is 17%. BRCA1 or BRCA2 alterations also increase the risk of breast cancer. ***See table-1 below.*** In addition, they can cause breast cancer in men, prostate cancer and pancreatic cancer. These risks are particularly linked to the BRCA2 gene.

More recently, other genes have been found to increase the risk of ovarian cancer. These have recently been found to be associated gene alterations which moderately increase the risk of ovarian cancer. These are known as 'moderate risk' genes. These genes include: **RAD51C, RAD51D, BRIP1** and **PALB2.** The risk of developing ovarian cancer up to the age of 80 years with an alteration in RAD51C is 11%, with RAD51D is 13%, with BRIP1 is 6% and with PALB2 is 5%. PALB2 is also associated with a high risk of breast cancer.

Women with gene alterations in **MLH1, MSH2, MSH6** and **PMS2** genes have an increased risk of womb cancer. The womb cancer risks with MLH1, MSH2, MSH6 range from 37% to 49%. The ovarian cancer risks range from 11% to 17%. PMS2 has a lower, though increased, risk of womb cancer of ~13%. It does not increase the risk of ovarian cancer. These four genes also increase the risk of bowel cancer.

Table 1:

LIFETIME CANCER RISKS %

GENE	Breast cancer	Ovarian cancer	Bowel cancer	Womb cancer
BRCA1	72	44		
BRCA2	69	17		
PALB2	53	5		
RAD51C		11		
RAD51D		13		
BRIP1		6		
MLH1		11	48	37
MSH2		17	47	49
MSH6		11	20	41
PMS2			14	13
General population risk (no altered gene)	12 % (1 in 8) to 15 % (1 in 7)	1,3 - 2 % (1 in 50)	5,6 % (1 in 18)	2,7 % (1 in 36)

Genetic testing

Who is eligible for genetic testing?

Gynaecological cancers are those which affect the womb, ovaries, cervix, vulva or vagina. There are many different types of these cancers. Most occur by chance and are not inherited. A small number are caused by faults in our genetic material, which may be passed down through families.

Our genetic material is made of DNA. DNA is our personal set of instructions on how to build the body. DNA is grouped together into genes.

Women with ovarian cancer

All women diagnosed with certain types of ovarian cancer (high grade epithelial ovarian cancer) should be offered genetic testing. This includes the majority of commonly diagnosed ovarian cancers. When women are diagnosed with ovarian cancer, the cancer tissue is routinely assessed in the laboratory by the pathologist. This tells you what type of cancer it is. Your doctor will tell you if your cancer type means that your cancer team will offer you genetic testing.

Women with womb or endometrial cancer

Women who develop endometrial cancer (cancer of the womb lining) have their cancer tissue tested in a laboratory. The pathologist also tests the cancer tissue with special stains for MLH1, MSH2, MSH6 and PMS2. This is called immuno-histochemistry (IHC). It is now recommended that all women with womb cancer have this test. This tests whether the genes produce proteins correctly. If the results show deficient staining for any of these genes, then gene function may be defective. In this case your doctors will offer you genetic testing. This helps determine if a genetic alteration (or Lynch Syndrome) has caused you to have this cancer.

In the situation where the stain for MLH1 gene is deficient, it may also occur due to another reason and not due to Lynch Syndrome. To exclude this, your doctor may ask for an additional test in this situation. This is called 'hyper methylation' testing. If the deficiency in the stain is due to 'hyper methylation', you will not need a genetic test.

People with a strong family history of cancer

Genetic testing has traditionally been offered to individuals with a strong family history of cancer. This usually means that several close relatives on the same side of the family have had a cancer linked to one of the genes above. Your doctor will let you know if you have a high-risk family history. You may get referred to a genetics expert such as a clinical geneticist or genetics counsellor for this assessment. They will guide you on your chance of carrying a gene alteration based on your family history.

If someone in your close family has been found to carry a gene alteration, you can be offered genetic testing for that alteration. This is called **predictive testing**.

Using family history alone may miss identifying a number of gene carriers. **Around 50% (half) of all individuals carrying an ovarian cancer gene alteration do not have a strong family history of cancer and may be missed.** For example, in women with Lynch Syndrome, using family history alone

may miss around 70% of individuals carrying a gene alteration. **Hence, all women with ovarian and womb cancer should now be offered genetic testing.**

Communities with raised risk of a cancer-predisposing gene

Certain communities have a higher presence of gene alterations. In the Jewish community, 30-40% of ovarian cancers and 10% of breast cancers are linked to the BRCA gene. Some healthcare systems may offer genetic testing to members of communities that are more likely to have gene alterations. Individuals of Jewish heritage may be able to have a BRCA test even without a family history of cancer. This is called "population-based testing" and is now being offered in Israel.

Who can offer me genetic testing?

Different countries or health care systems offer genetic testing in different ways. This may at times also vary among hospitals in the same country.

Many countries use a *genetic assessor or genetic counsellor*, or **genetics clinician driven system**. This means your doctor will assess if you are eligible for genetic testing. The decision will be based on information about cancers in your family, or on your type of cancer. You will see a genetic assessor or genetic counsellor or clinical geneticist for counselling and undergoing genetic testing. You can decide together with the expert if you want to proceed with testing. If the test finds an alteration or mutation, you can discuss what this means for your treatment or care with your doctor.

Another approach is a **'mainstreaming approach'**. This approach allows counselling to be performed and testing undertaken by a non-genetics clinician. This is usually your treating clinician such as a medical oncologist, surgical oncologist, or clinical nurse specialist, who have been trained to counsel on this issue. This is done for all women with epithelial ovarian cancer. Recently, it has also been recommended for women who have possible characteristics of inherited womb cancer. This means your doctor or clinical nurse will discuss with you the potential benefits and pitfalls of testing. If you decide to have a genetic test and the test finds an alteration you may then be referred to a clinical genetics team. This approach for women with cancer has been used in the United Kingdom and other countries to improve access to testing. This also reduces the workload and waiting for counsellors.

How is a genetic test performed?

This can be done using a blood sample, just like a routine blood test. DNA from the blood is then tested in the laboratory to find gene alterations.

In some cases, gene testing can be done from a sample of saliva. If this is offered, you might even be able to do the test at home with a kit. It is important that testing is undertaken by an accredited laboratory.

Testing using a blood or saliva sample is called **germline testing**.

Women who have developed ovarian cancer are also offered genetic testing of the tumour tissue. Testing of the tumour tissue is called **somatic testing**.

Only gene alterations found in the germline (blood or saliva) can be inherited. If a gene alteration is found in the blood, this means it has come from a person's parents, and can be passed on to children.

If the gene alteration is found in the cancer tissue 'only', through somatic testing, but not in the blood, then it is not inherited. This means it cannot be passed on to other family members. However, it can help guide treatment as well as give you the opportunity to use newly developed treatments.

Testing tumour tissue can be done at the same time as germline testing. It can also be done before or after germline testing.

Parallel Testing: Both **germline and somatic** testing is recommended for women with ovarian cancer eligible for genetic testing.

What are the possible outcomes of a genetic test?

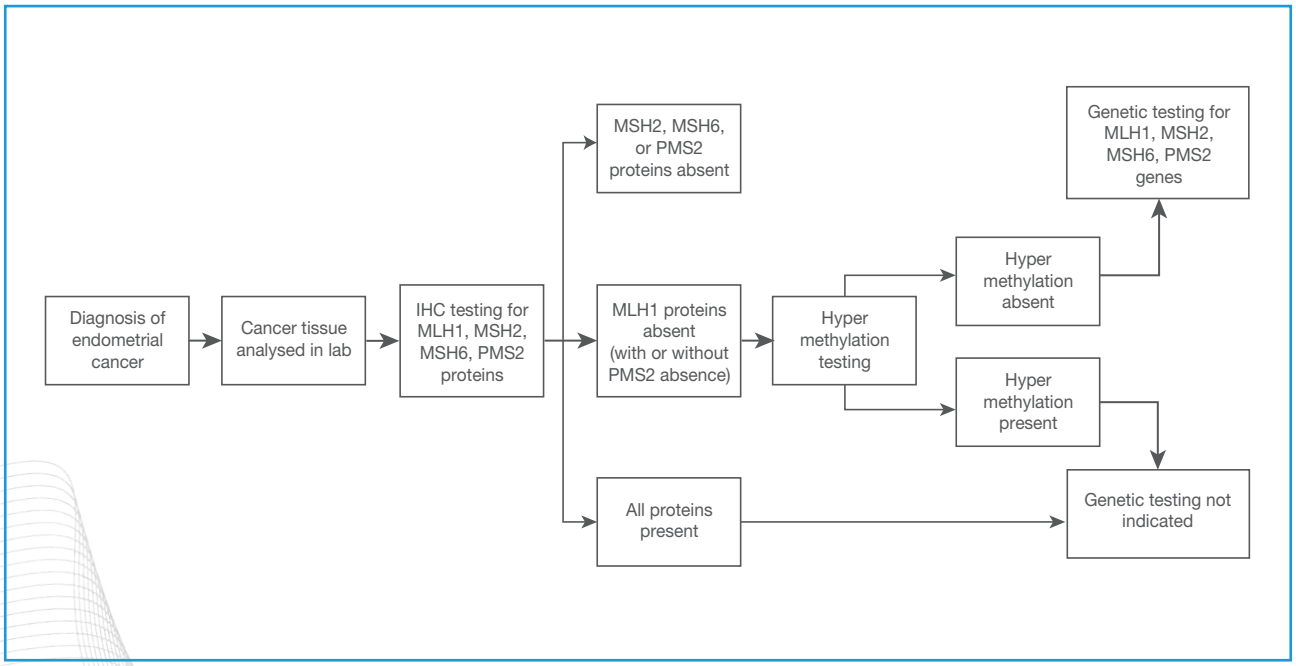
Genetic test results should be given to you by a trained professional. In essence there are three possible outcomes.

a) **Positive result** – the result shows a significant alteration in a gene tested. These are often described as 'pathogenic' or 'likely pathogenic' in your report.

b) **Negative result** – the result does not show an alteration to explain the cancer. There may be no alteration. Or at times an alteration is found but is described as 'benign' or 'likely benign'. This means that any error in the gene code that was identified does not affect its function and is not the cause of the cancer. It is treated as a negative result.

c) **Variant of Uncertain Significance (VUS):** The test finds an alteration that is difficult to interpret. It is currently treated as negative with no immediate implication. But its category may change in the future. Over time, in a small proportion of people, this gene alteration can be reclassified as a cause of the cancer.

See figure below:



The 3 possible outcomes of a genetic test, depicted in the Table 2.

Table 2:

TYPE OF OUTCOME	
Positive test result	This means there is an alteration in one of the genes that increases someone's cancer risk. This suggests that the cancer is caused by this faulty gene. This result may: a) help you decide on treatment or surgery to reduce your risk of cancer if you do not have cancer. b) allow you to make decisions about your treatment, if already diagnosed with cancer. c) support genetic testing of relatives and allow them to reduce their cancer risk.
Negative test result	This means there was no identified cancer-causing alteration in the genes.
Variant of Unknown Significance (VUS)	Sometimes genetic tests find alterations in the genes that cannot be interpreted in a meaningful way. This occurs occasionally and is called a Variant of Unknown Significance (VUS). For most women this type of result will not have significant implications. Relatives do not need to be offered genetic testing for a VUS. No screening or prevention should be undertaken for a VUS. Over time, in a small proportion of people, these gene alterations can be reclassified, and we may learn that this is actuallly the cause of the cancer.

What happens if I test negative?

If you test negative the result shows that your cancer is not caused by one of the altered genes that you were tested for. It is very likely that you have a low risk of developing other cancers. Your risk is likely to be similar to the rest of the general population. However, you are only "negative" for the alterations you were tested for, so be aware of which genetic alterations were tested since genetic testing is developing overtime.

You should continue to have cancer screening just as everyone else (such as mammogram screening for breast cancer for women over 50).

If you test negative, but there are several other cancers in the family, and you fulfil certain 'high-risk' criteria, you should still see a genetics expert. They will assess your risk based on your family history itself. They may offer further advice based on implications of your risk.

General considerations in genetic testing

What are the advantages of genetic testing?

Genetic testing can be helpful to the person taking the test.

THE ADVANTAGES ARE:

- The result can provide information to you on your risk of developing cancer.
- It may reduce your anxiety about knowing your risk or reason for having cancer.
- It may enable you to take steps to help prevent a second cancer if an inheritable altered gene is identified.
- If an altered gene is identified, you can provide valuable information to your relatives. This can enable other family members to have genetic testing to find out their cancer risk. They can then take proactive steps to reduce their cancer risk through screenings and risk reducing surgeries.
- If you already have cancer, the test outcome could help your doctors choose the best treatments for your specific type of cancer.

What are the disadvantages of genetic testing?

There are some potential disadvantages with genetic testing.

THESE ARE:

- Some people who receive a positive test result can feel frightened, sad, or emotionally upset about the result.
- Some people experience guilt due to passing gene alterations on to their children.
- A positive test result can cause a strain on personal relationships.
- In some communities, a positive test result might lead to social exclusion or poor marriage prospects.
- You should check if your test result can affect your insurance. Safeguards exist in some countries which protect insurance premiums of patients who have a gene alteration.

It is important to explore all the benefits and disadvantages. You should carefully consider them before deciding to undergo genetic testing.

Implications of a positive test result

A positive result means a gene alteration is present. The gene alteration increases your risk of developing a second cancer. This can help you decide on further actions you want to take to reduce your risk. For example, women with a BRCA1, BRCA2 or PALB2 gene alteration have an increased risk of developing breast cancer. While women with Lynch Syndrome have an increased risk of developing bowel cancer. This can help you choose to have increased surveillance tests or take action to decrease the risk. It may also influence treatment options for your cancer. Your relatives can have genetic testing for the same gene alteration. If found to have inherited it, they can opt for screening or prevention options to reduce risk.

Implications of a negative test result

A negative genetic test means the likelihood of you developing a hereditary cancer is low. Your risk is probably similar to the general population. Research with patients shows that a negative test result is associated with reduced cancer worry and anxiety. Even if you do not have a positive test result, you should still attend the screening programmes available to you (e.g., breast cancer or cervical cancer screening).

How confidential is a genetic test?

Results of a genetic test are confidential. You can decide who you want to share the results with.

Implications of genetic testing for individual cancers

1. OVARIAN CANCER

Ovarian cancer develops in 1 in 50 women. Most ovarian cancers are not linked to gene alterations. However, up-to 1 in 5 ovarian cancers are linked to gene alterations and can run in families. Most women who develop ovarian cancer are over 50 years of age. Women have usually been through menopause by the time the disease is found. Alterations or mutations in the genes BRCA1/BRCA2, PALB2, RAD51C, RAD51D and BRIP1 are associated with an increased risk for ovarian cancer, at a younger age. Lynch syndrome genes MLH1, MSH2 and MSH6 are also associated with an increased risk of ovarian cancer. If you have been diagnosed with ovarian cancer, you are likely to be offered both germline and somatic testing.

GENETIC TESTING IF YOU HAVE BEEN DIAGNOSED WITH OVARIAN CANCER

Germline testing in ovarian cancer: This will involve a DNA test using a blood or saliva sample.

Somatic testing in ovarian cancer: Tumour tissue is tested routinely for alterations in BRCA genes. Additionally, in some centres your oncologist may recommend **HRD testing**. HRD test identifies women whose tumour tissue harbours defects in the HRD pathway. This includes other genetic defects included in other genes contributing to this pathway. This trait has also been called "BRCAness". These women also benefit from PARP inhibitor treatment. This can identify many more women who can benefit from PARP inhibitor treatment than just the BRCA test. Testing tumour tissue can be done at the same time as germline testing. It can also be done before or after germline testing.

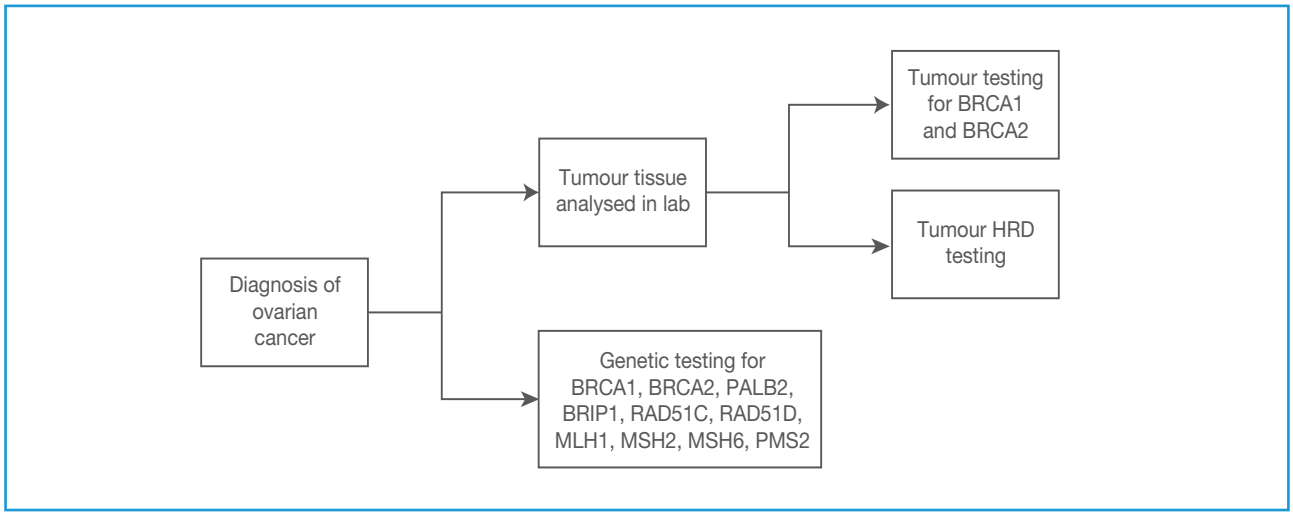
Parallel Testing: Both germline and somatic testing is recommended for women with ovarian cancer eligible for genetic testing. This is called parallel testing.

What happens if I test germline positive and I have ovarian cancer?

A positive result indicates that you have inherited one of the known gene alterations associated with ovarian cancer. You will be referred to your genetics service.

- The result will tell you if you carry an alteration in one of the ovarian cancer genes in Table 1.
- If you carry an alteration in the BRCA1 or BRCA2 genes it may affect the treatment you receive in the future. You may be able to get a drug called a PARP inhibitor.
- If you carry a gene alteration, you may be eligible to take part in new drug treatment trials. Your doctor will be able to give you further information on this.
- If you carry an alteration in the BRCA1, BRCA2 or PALB2 genes you are at high risk of breast cancer too. You would be able to opt for more intensive high risk breast cancer screening or risk reducing options. This will help minimise your risk of breast cancer.

- You will receive post-test counselling support and should consider speaking to a genetics expert if you have not done so already.
- You may want to alert your relatives. Members of your family or relatives can undergo genetic testing. This will help them find out if they too carry this gene alteration and are at high risk. Those found to do so can access relevant early detection and preventive options to minimise their risk.



What happens if I test somatic positive and I have ovarian cancer?

This means there is an alteration in your tumour tissue. It is important for you to have a germline test too, if you have not done so. If this alteration is present in the germline, then it is inheritable with the implications described above. If this alteration is absent in the germline, then it cannot be inherited or passed on to your children. This will have implications for your treatment. You can access new drugs called PARP (poly ADP-ribose polymerase) inhibitors. This reduces the risk of the cancer coming back.

How will the test result affect my ovarian cancer treatment?

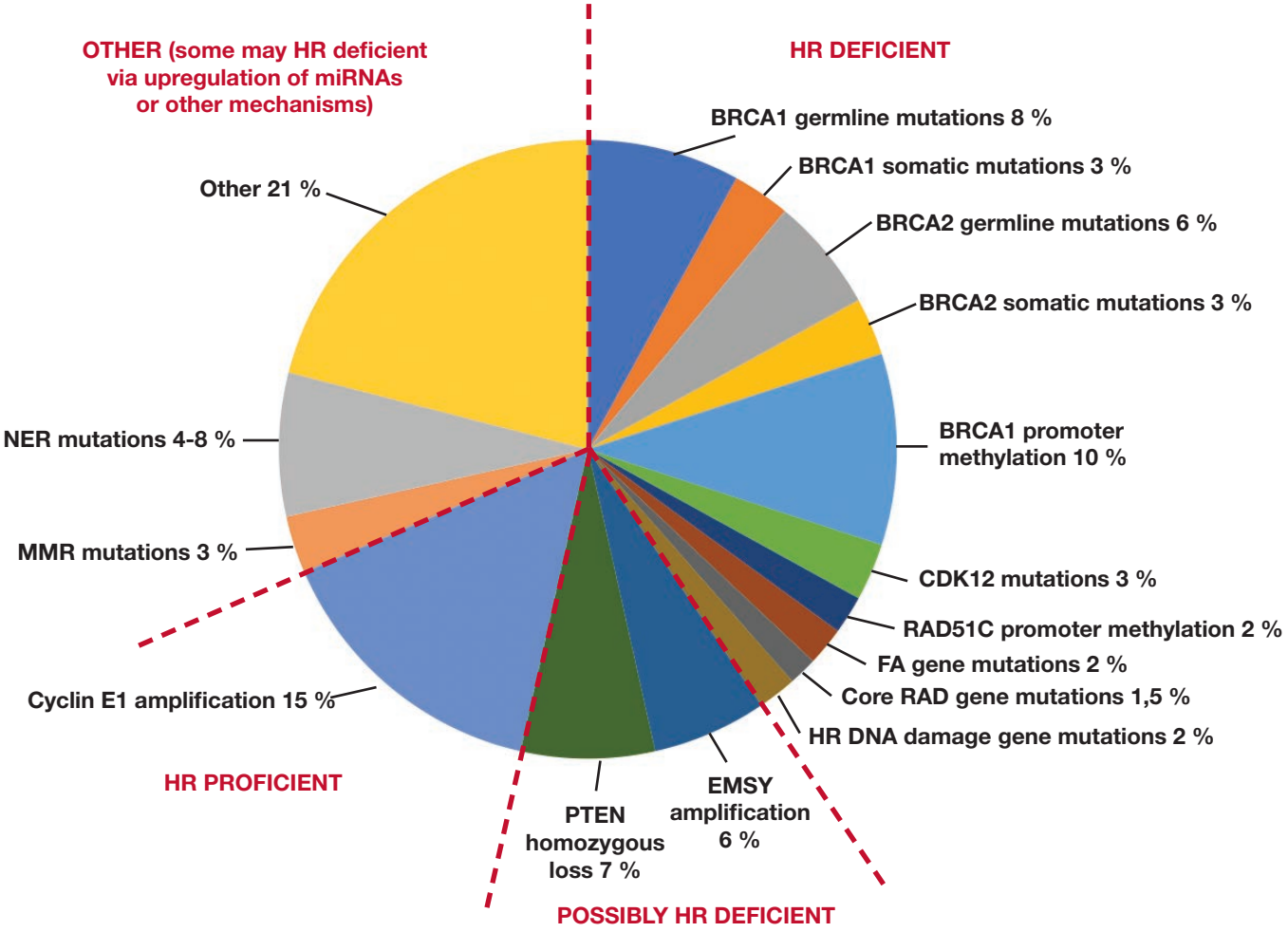
This test result allows your doctor to personalise and target your cancer treatment.

PARP inhibitors are one such type of drug. They block enzymes involved in repairing damaged DNA. These drugs have been shown to fight cancers caused by alterations in BRCA1 and BRCA2 genes. They also benefit women whose cancer has defects in the broader HRD pathway. HRD stands for Homologous Recombination Deficiency. According to national guidelines, you may be eligible for PARP inhibitor treatment if your test result shows an alteration in the BRCA genes or the HRD test result is positive. Talk to your oncologist about this.

You may be eligible to take part in new drug treatment trials. Your doctor or treating healthcare team will be able to give you further information on this.

In some cases, it is possible your oncologist may offer you PARP inhibitor treatment even if the test result is negative. Your oncologist will discuss this with you.The access to receiving parp inhibitor treatment varies from country to country.

Below is an overview of the mutations in patients with high-grade serous ovarian cancer.



Source: Konstantinopoulos PA, Ceccaldi R, Shapiro GI, D'Andrea AD. Homologous RecombinatIon Deficiency: Exploiting the Fundamental Vulnerability of Ovarian Cancer. Cancer Discov. 2015 Nov;5(11):1137-54. doi: 10.1158/2159-8290.CD-15-0714. Epub 2015 Oct 13.

Explanation of the pie chart:

On the right-hand side of the pie chart, you will see the BRCA mutations, which amount to about 20% of the cases of high-grade serous ovarian cancer (if the mutation is measured in blood, it is hereditary. If the mutation is measured in the cancer tissue, it is somatic (not hereditary). Below these are the other gene mutations which make up-to 30% of the ovarian cancer cases. They encompass the so-called HRD positive patients (HR deficient). The other half of the patients on the left-hand side of the pie chart are the so-called HRD negative patient (HR proficient).

PARP-inhibitors are most effective on the 50 % of the patients that either have a BRCA-mutation or are HRD positive, called "BRCAness". There is however, also an effect in the HRD negative group of patients, so some PARP-inhibitors are also approved by EMA (European Medicines Agency) for these patients.

OPTIONS FOR REDUCING THE OVARIAN CANCER RISK

This section is relevant for family members who are at high risk of developing ovarian cancer. There are options available to reduce the risk of cancer. Your doctor will provide you with information to understand your cancer risk.

Reproductive, lifestyle choices and medical prevention

Oral Contraceptive pill: There is good evidence to show that using the combined (oestrogen and progesterone) oral contraceptive pill reduces the risk of ovarian cancer. The level of risk reduction increases with the increasing duration of use. Available data from high-risk populations suggest that similar benefits are found in BRCA1/BRCA2 carriers who take the contraceptive pill. Some studies indicate a 50% reduction in risk with 5 years' use. Benefits persist for many years after stopping the pill though the level of benefit decreases with time since stopping the pill.

The impact of pill use on breast cancer risks in BRCA1/BRCA2 carriers is less well understood with a number of studies evaluating this showing conflicting results. Some studies do not show an increased risk while others do suggest an increase in risk. While using the combined pill may be associated with an increase in breast cancer risk, the actual (absolute) increase in risk may be small, particularly for much younger users. The pill is contraindicated in women who have had breast cancer.

The decision to take the pill (or not) should be made following discussion with your doctor. You should consider the benefits and risks as well as your medical history, and other alternative contraception methods. This should help you decide what is the best way forward for you.

Preimplantation genetic diagnosis (PGD): Some women of childbearing age with an inheritable genetic alteration might wish to consider preimplantation genetic diagnosis (PGD) to avoid passing their genetic alteration on to their children. It is a technique which involves assisted conception through In Vitro Fertilisation (IVF). Embryos developed via IVF are biopsied and tested for the genetic alteration in the family. Embryos that do not have the genetic alteration and are considered suitable are transferred to the womb to establish a pregnancy. Access to PGD varies from country to country.

Surgical prevention

Surgical prevention of ovarian cancer involves the removal of both the tubes and ovaries. This is called salpingo-oophorectomy. It is offered to women with an increased risk of ovarian cancer. It is usually undertaken by keyhole surgery once childbearing is complete. Surgery is usually performed after the age of 35 onwards. This is offered when the risk of cancer begins to rise. In women with early onset ovarian cancers in the family it may be undertaken five years before the appearance of ovarian cancer in your family. This can significantly reduce your risk of ovarian cancer. A very small risk of peritoneal cancer (cancer of the abdominal lining) may persist. This cancer behaves similar to ovarian cancer.

Early removal of the ovaries in pre-menopausal women will start menopause. This can cause symptoms such as hot flushes, night sweats, alteration in mood / concentration, vaginal dryness, or sexual problems.

Early menopause may also lead to thinning of bones and heart problems later in life. These undesirable effects can be reduced by hormone replacement therapy. This is safe in women who have not had breast cancer and have no other contraindications. It is recommended until the age of 51 years (average age of menopause) in women who undergo early surgical menopause. Please discuss this with your doctor.

Scientists now believe that most ovarian cancers arise in the tubes. A new alternative to reduce ovarian cancer risk is being investigated. This can avoid the onset of early menopause. This involves two operations. In the first step, the fallopian tubes are removed. This is called Early Salpingectomy. This reduces the risk of ovarian cancer but does not cause early menopause. In the second step, the ovaries are removed. The removal of the ovaries can happen at a later time according to the wish of the patient or at the natural age of menopause. This is called delayed oophorectomy. The precise level of risk reduction from removing tubes alone remains unknown. This is currently only advisable in a research study setting.

This may be an important method for young women, who are at high risk of ovarian cancer and want to reduce their risk but would delay surgery due to concerns about early menopause. It enables these women to obtain some risk reduction while preserving ovarian function and delaying onset of menopause. It should only be undertaken within a research study and is being offered to women from the age of 30 years onwards.

Screening or surveillance for ovarian cancer

Screening for ovarian cancer is currently not available. Large studies have looked at this in the general population of women. These studies have used ultrasound and Ca125 blood tests. Sadly, it was not shown to save lives.

Annual screening by ultrasound or Ca125 blood test is not beneficial in high-risk women and is not advised/recommended. More frequent 4 monthly screening for ovarian cancer using a Ca125 based mathematical algorithm has been investigated in high-risk women. This has been shown to identify cancers earlier in women who preferred to delay surgical prevention. Although screening may detect cancer earlier, it currently remains unavailable as a screening programme given the uncertainty around the benefit of saving lives.

2. WOMB (ENDOMETRIAL) CANCER

Endometrial or womb cancer is cancer of the lining of the womb. It is the most common gynaecological cancer. Usually, it develops after menopause. Women are typically diagnosed in their 60s. 3% (1 in 33) of all womb cancers are related to gene alterations. The most common cause is a condition called Lynch syndrome. This is where there are alterations in genes which repair DNA, called mismatch-repair genes. These genes are MLH1, MSH2, MSH6 and PMS2. If you are found to have Lynch syndrome, there is also an increased risk of other cancers. The most common cancers associated with Lynch syndrome are womb, bowel, and ovarian cancer. There is also a small increased risk of cancers of the stomach, urinary tract, pancreas, and brain. Screening for early diagnosis is available for some Lynch syndrome cancers in some European countries.

GENETIC TESTING IF YOU HAVE HAD ENDOMETRIAL OR WOMB CANCER

What happens if I test germline positive and I have had womb cancer?

This means you have an alteration in MLH1, MSH2, MSH6 or PMS2 genes. This is called Lynch Syndrome.

- You have an increased risk of bowel (colorectal) cancer.
- Regular, high quality bowel screening using colonoscopy can reduce your cancer risk. This is recommended every two years.
- Aspirin has also been shown to reduce bowel cancer risk. It is recommended in Lynch Syndrome. It may also be beneficial in reducing the risk of other Lynch syndrome cancers. The decision to take aspirin should be made with your doctor.
- Testing for a stomach bacteria called H pylori, followed by a course of antibiotics in people who have these bacteria, may reduce your lifetime risk of stomach (gastric) cancer.
- Healthy lifestyle may reduce the risk of bowel or other non-gynaecological cancers, for example regular exercise, maintaining a healthy weight or a diet rich in fibre.
- You may want to alert your relatives. Members of your family or relatives can undergo genetic testing. This will help them find out if they too carry this gene alteration and are at high risk. Those found to have this alteration, can access relevant early detection and risk reducing options to minimise their risk.
- You may wish to speak to a genetics expert, (genetics counsellor or clinical geneticist) if you have not done so already.

Options for reducing risk of endometrial cancer

This section is relevant for family members who have Lynch Syndrome and have not had endometrial cancer. There are options available to reduce the risk of cancer. Your doctor will provide you with information to understand your cancer risk.

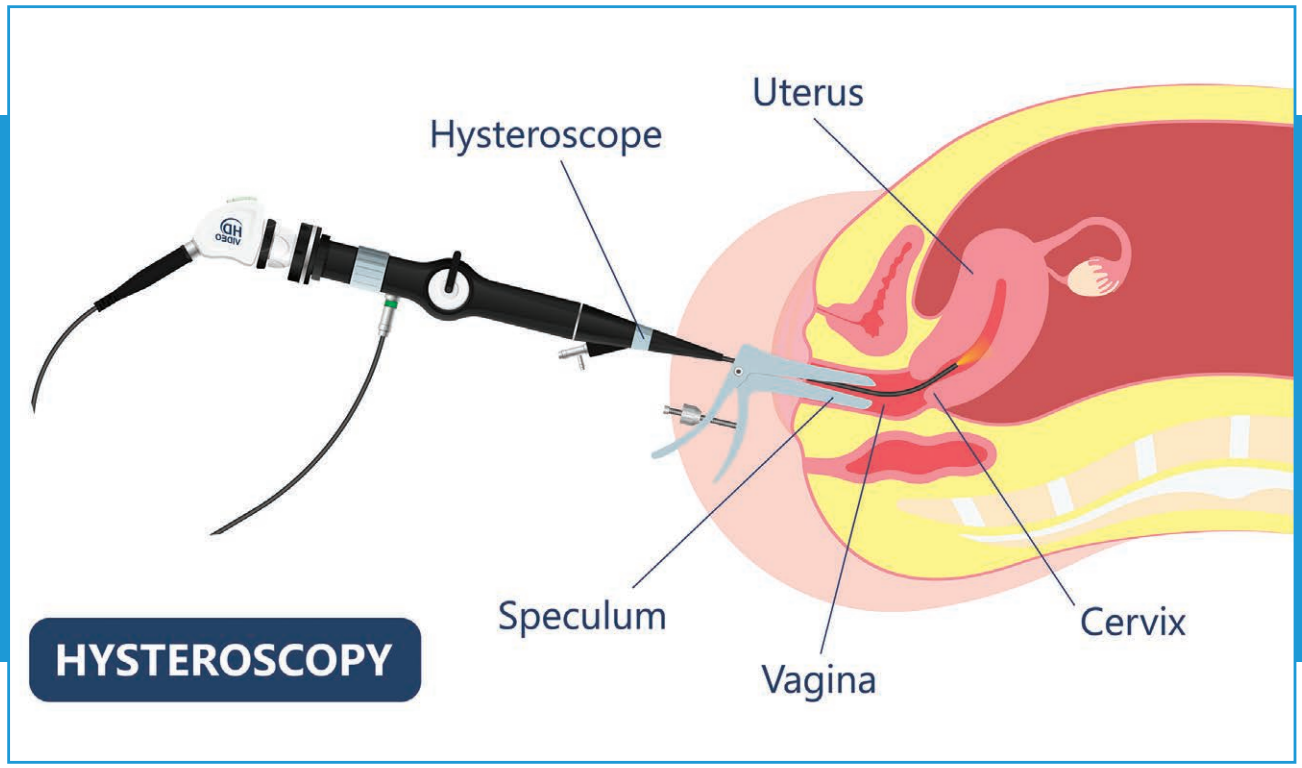
Medical prevention

Aspirin is recommended for women with Lynch Syndrome. Although data specific for endometrial cancer risk are lacking, it does reduce bowel cancer risk and overall cancer risk in women with Lynch Syndrome.

Research shows that the oral contraceptive pill also reduces the risk of womb (endometrial) cancer. The decision to take the pill should be made with your doctor. You should consider the benefits as well as your medical history, and other contraception methods. An intrauterine device containing the progesterone hormone (also called a hormonal coil), which is placed in the womb, can reduce the risk of endometrial cancer. It can also serve as a contraceptive. In some women it is also used to control symptoms of heavy bleeding. However, data specific to women with Lynch Syndrome are lacking.

Screening or surveillance and surgical prevention

In women at risk for Lynch syndrome, regular screening for bowel cancer is recommended. This is called colonoscopy. These bowel checks should be done every 2 years. Carriers of MLH1 or MSH2 gene mutations should have regular colonoscopies from 25 years of age. Carriers of MSH6 or PMS2 gene mutations should have colonoscopies from 35 years of age. This has been shown to reduce the risk of bowel cancer. After hysterectomy, some women may experience increased discomfort during colonoscopy. However, comfort during colonoscopy is important and colonoscopy is usually carefully managed, since a good experience is key to ensuring that people with Lynch syndrome have this cancer preventing check-up.



Screening may be offered for endometrial cancer from the age of 35 in some countries. This involves annual scans and sampling of the womb lining. The sample may be undertaken at time of a hysteroscopy. This involves inspection of the womb with a fine telescope. Data on the benefit of screening for endometrial cancer are limited. While screening can detect pre-cancer and early cancer, there is no data showing it saves lives. Further research is needed in this area. Please discuss the pros and cons of surveillance / screening with your doctor.

Women are also advised to keep a menstrual calendar and any abnormal bleeding should be promptly investigated.

Surgery is extremely effective in preventing endometrial and ovarian cancer in women with Lynch syndrome. Removal of the womb prevents endometrial cancer. Surgical prevention in Lynch Syndrome involves a hysterectomy which is the removal of the womb as well as removal of the tubes and ovaries. This is because women with Lynch Syndrome are also at an increased risk of ovarian cancer (except women who have a PMS2 gene alteration). This is usually offered from the age of 40 years. Women who have early surgical menopause are advised HRT (Hormone Replacement Therapy) till the age of 51 years if there are no other contraindications.

3. PREVENTING HEREDITARY BREAST CANCER

Breast cancer represents the most common type of cancer in women. The risk of developing breast cancer without a genetic fault is 1 in 7 women. Some genes that increase the risk for ovarian cancer are also connected to a high risk of developing breast cancer. These genes are BRCA1, BRCA2 and PALB2. The risk for developing breast cancer (till age 80 years) for carriers of BRCA1 mutations is 72%, for BRCA2 mutation carriers 69 % and for PALB2 carriers 53 %.

Additionally, there are some other breast cancer genes which are associated with a moderate risk of breast cancer. These include the ovarian cancer genes RAD51C and RAD51D. The breast cancer risk with RAD51C is 21% and with RAD51D 20%. All women should regularly check their breasts, irrespective of the presence of a gene alteration.

Women carrying one of the genetic alterations have options for screening and risk reduction options for breast cancer. You should see a genetics specialist (clinical geneticist or genetics counsellor) and relevant breast specialist to discuss your risk and risk management options. These specialists will take the gene alteration you may carry as well as your family history into consideration.

Screening and early detection

More intensive screening for breast cancer is recommended for women who have a high-risk cancer predisposing gene for breast cancer or a strong family history of breast cancer. Following specialist risk assessment this may also be offered to some women with moderate risk genes, particularly if accompanied by a strong family history of cancer. The most common type of imaging for breast cancer screening is mammography. This is a type of breast x-ray. This imaging modality is used for women above 40 years of age. In women younger than 40 years, mammograms are not often used, as breast tissue can be dense. Dense breast tissue makes changes harder to identify and is therefore not the optimal imaging technique in young women. Young women at high risk for breast cancer will be offered annual MRIs from the age of 30 years to 50 years and then mammograms thereafter. This may vary from country to country.

Medication to prevent breast cancer

If you have not had breast cancer and are also not considering risk reducing surgery for breast cancer, you may be offered chemoprevention. Chemoprevention means the use of medication to reduce cancer risk. Research shows that a 5 year course of medication like Tamoxifen, Raloxifene or Anastrazole can lower breast cancer risk. The decision to undergo chemoprevention should be done after consideration of risks and benefits and a discussion with your doctor.

Risk Reducing Surgery

Women with high risk of breast cancer (usually >30-40% lifetime risk) can also decide to undergo bilateral risk-reducing mastectomy (removal of both breasts). During a mastectomy breast tissue is removed in order to reduce breast cancer risk. The decision to undergo this operation should be done after counselling by a specialist breast surgeon. You will have the option to also consider reconstructive breast surgery as part of or after your mastectomies. Mastectomy can reduce the risk of breast cancer by 90-95%.

Glossary

DNA – Deoxyribonucleic Acid

Gene mutation – error or alteration in a gene

PARP inhibitor - Poly (ADP-ribose) polymerase inhibitors are a novel class of anti-cancer therapy used in ovarian cancer management

Germline testing – testing of non-cancer cells in blood, saliva or other material in order to determine the presence of cancer predisposing genes

Somatic testing – testing of tumour tissue for genetic mutations

Parallel testing – testing tumour tissue can be done at the same time as germline testing

PGD – preimplantation genetic diagnosis, an in vitro fertilization procedure to prevent the passing of genetic mutations to their children

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ESGO European Network of Gynaecological Cancer Advocacy Groups

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Prof. Dr. Ranjit Manchanda (UK), Dr. Ashwin Kalra (UK),
Dr. Kevin Monaghan (UK), Dr. Sam Oxley (UK), Dr. Michail Sideris (UK),
Dr. Monika Sobocan (UK, Slovenia), Ms Tracie Miles (UK),
Lisa Cohen (Israel) and Birthe Lemley (DK).

Contact information of ENGAGe

Webpage: https://engage.esgo.org/
Email: engage@esgo.org
Facebook: https://www.facebook.com/engage.esgo

ENGAGe recommends contacting your local patient association!

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