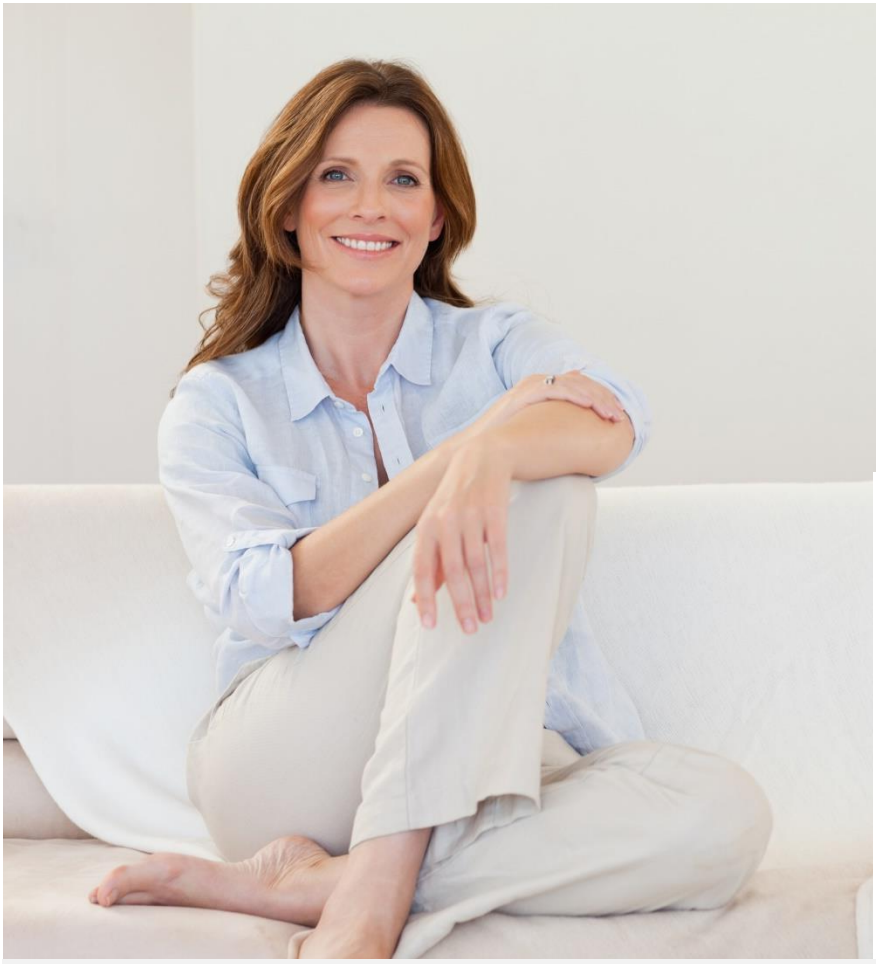
otogenetics®
corporation



Information About Your Hereditary Cancer Risk Assessment

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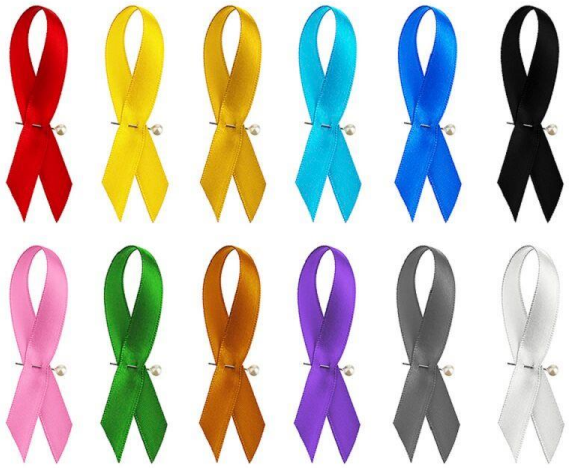
Discovery Diagnosis Better Health Outcomes

What Is Cancer?

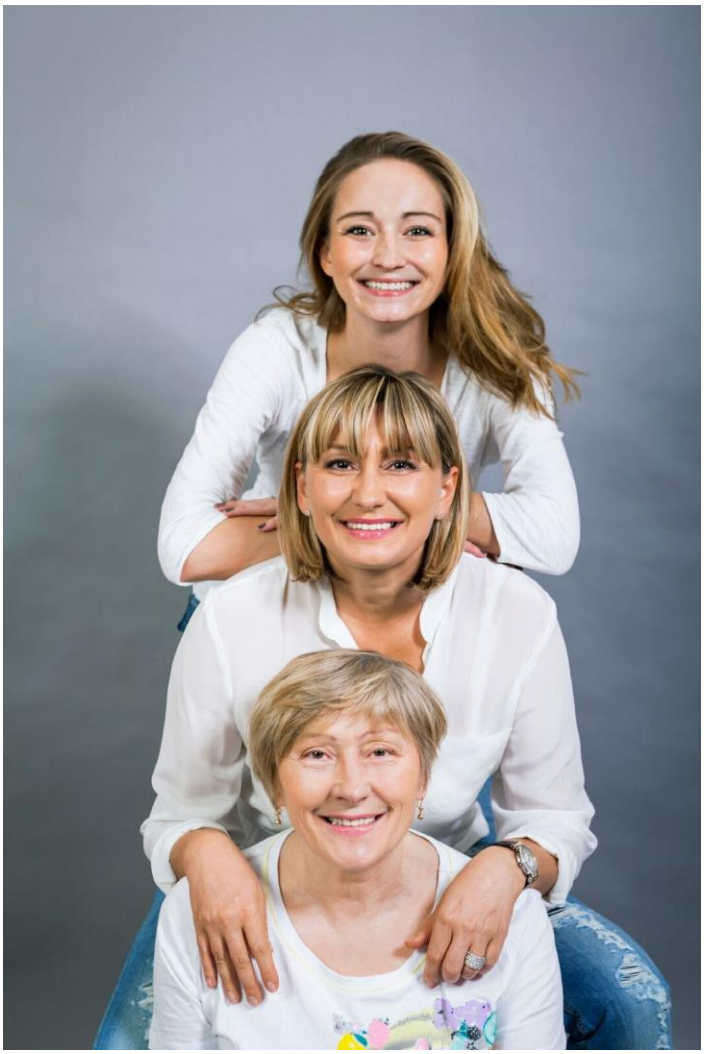


Cancer is class of disease where there is uncontrolled growth of abnormal cells in the body. Cancer develops when the body's normal process of cell growth goes wrong and new cells form when the body doesn't need them and old or damaged cells do not die as they should. Buildups of these abnormal cells often invade healthy cells and may form a mass of tissue, called a lump, growth or tumor.

There are some cancers, like leukemia, cancer of the blood that does not form tumors. They grow in the blood cells or other cells of the body.

Cancer Is Not Just One Disease

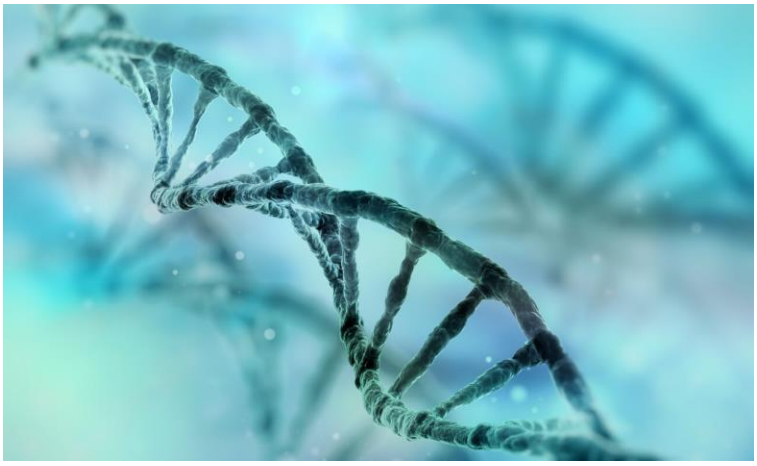
There are many types of cancer. It's not just one disease. Cancer can start in the lungs, breast, colon, or even in blood. Cancer cells can also spread to other parts of the body. For instance, cancer cells in the lung can travel to the bones and grow there. When cancer cells spread, it's called metastasis. When lung cancer spreads to the bones, it's still called lung cancer. It's not called bone cancer unless it started in the bones.



Cancer And Genetics

Cancers that run in families can be caused by an abnormal gene that is passed from generation to generation. Although this is often referred to as inherited cancer, what is inherited is the abnormal gene that can lead to cancer, not the cancer itself. Only about 5 to 10% of all cancers are thought to result directly from gene defects or mutations inherited from a parent.

Gene Mutations Can Be Inherited Or Acquired



An inherited gene mutation is present in the egg or sperm cell that formed the child and is passed down through generations.

An acquired gene mutation does not come from a parent, but is acquired some time later. It starts in one cell, and then is passed on to any new cells that are created from that cell. This kind of mutation is not present in egg or sperm cells, so it is not passed on to the next generation. Acquired mutations are much more common than inherited mutations. Most cancers are caused by acquired mutations.

Most cancer occurs by chance. In some families we see more cancer than we would expect by chance alone. In families that carry a genetic change or mutation that is associated with causing cancer, the cancer risk is much higher than that of the general population. Genetic testing helps to determine which of these families have cancer that is related to an inherited gene mutation.

Sporadic Cancer – Cancer which occurs by chance. People with sporadic cancer typically do not have relatives with the same type of cancer.

Familial Cancer – Cancer likely caused by a combination of genetic and environmental risk factors. People with familial cancer may have one or more relatives with the same type of cancer or related types of cancers; however, there does not appear to be a specific pattern of inheritance (e.g., the cancer risk is not clearly passed from parent to child). In families where the risk of breast cancer is moderately or just slightly increased, the relationship between affected family members is more distant and the age of diagnosis later.

Hereditary Cancer – Cancer occurs when an altered gene (genetic change or mutation) is passed down in the family from parent to child. People with hereditary cancer are more likely to have relatives with the same type or a related type of cancer. They may develop more than one cancer and their cancer often occurs at an earlier than average age.

It may be difficult to distinguish between hereditary and familial forms of breast

cancer. The contribution of genetic mutations is best regarded as a continuum: in familial breast cancer genetic abnormalities play a minor role in the risk of breast cancer, whereas in hereditary forms, BRCA1 and BRCA2 mutations have a significant impact. Many families, however, find themselves caught at the boundary between these two entities.

Risk Factors

Certain things make it more likely that cancers in a family are caused by a family cancer syndrome, such as:

- Many cases of the same type of cancer, especially if it is an uncommon or rare type of cancer.
- Cancers occurring at younger ages than usual such as colon cancer in a 20-year-old.
- More than one type of cancer in a single person such as a woman with both breast and ovarian cancer.
- Cancers occurring in both of a pair of organs like both eyes, both kidneys, or both breasts.
- More than one childhood cancer in siblings for example sarcoma in both a brother and a sister.
- Cancer occurring in the gender not usually affected such as breast cancer in a man.
- Cancer occurring in many generations, like in a grandfather, father, and son.

When trying to determine if cancer might run in your family, first gather some information. Look at:

- Who has the cancer? How are you related? Which side of the family are they on (mother's or father's)?
- What type of cancer is it? Is it rare?
- How old was this relative when they were diagnosed?
- Did this person get more than one type of cancer?
- Did they have any known risk factors for their type of cancer (such as smoking for lung cancer)?

Examples Of Hereditary Cancer Syndromes

Breast Cancer is the most common cancer in women in developed countries, affecting about 1 in 8 (12.5%) women in their lifetime. The National Cancer Institute

(NCI) estimates that approximately 231,840 new cases of female breast cancer and 2,350 new cases of male breast cancer will be diagnosed in the U.S. in 2017.

Ovarian Cancer is the fifth most common cancer among women in developed countries, affecting approximately 1 in 71 (1.4%) women in their lifetime.

Colorectal Cancer (CRC) affects about 1 in 20 (5%) men and women in their lifetime. The NCI estimates that ~132,700 new cases will be diagnosed and ~49,700 CRC deaths will occur in the U.S. in 2017.

Uterine Cancer affects about 1 in 38 (2.6%) women in their lifetime. The NCI estimates that approximately 54,870 new cases of uterine cancer will be diagnosed and ~10,170 uterine cancer deaths will occur in the U.S. in 2017. Increased risk for uterine cancer has been identified in a number of hereditary cancer syndromes, including Lynch syndrome and Cowden syndrome.

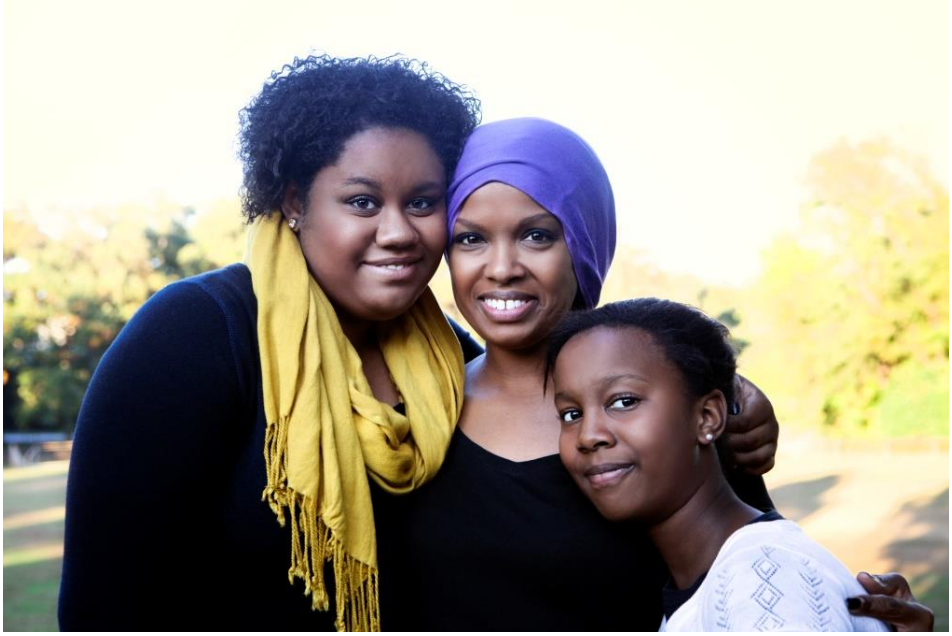
Prostate Cancer is the second most common cancer in men in the United States, after skin cancer. The NCI estimates that approximately 180,890 new cases of prostate cancer will be diagnosed in the U.S. in 2017. Hereditary prostate cancer may be diagnosed at younger ages and may also be more aggressive. For example, BRCA1 and BRCA2 gene mutations have been shown to be associated with more aggressive prostate cancer.

What Is Hereditary Breast And Ovarian Cancer (HBOC) Syndrome?

HBOC syndrome is an inherited genetic condition. This means that the cancer risk is passed from generation to generation in a family. If you have HBOC syndrome, you carry a gene mutation you inherited from your father or your mother, or sometimes from both parents, that significantly increases your risk for certain cancers. Hereditary Breast and Ovarian Cancer (HBOC) syndrome can be inherited from either the father's side or the mother's side of the family.

What Causes HBOC?

BRCA1 and BRCA2 (BReast CAncer genes 1 and 2) are the most well-known genes linked to breast cancer risk and are associated with the majority of HBOC families.



BRCA1/2 mutations can be passed to you from either parent and can affect the risk of cancers in both women and men.

Inherited mutations of either the BRCA1 or BRCA2 gene causes about 10% of breast and ovarian cancers. Other, less common genes have also been associated with an increased risk of developing breast and other cancers, such as mutations in the TP53, PTEN, CDH1, ATM, CHEK2 or PALB2 tumor suppression genes. The BRCA1 and BRCA2 genes normally help regulate cell growth. A person who has a BRCA1/2 mutation is sometimes called a BRCA1/2 carrier.

A mutation or alteration in either BRCA1 or BRCA2 increases a woman's lifetime risk of developing breast and ovarian cancers.

A person with BRCA1/2 mutations not only has a higher risk of developing these cancers, but also may pass that gene mutation on to his or her children.

Men with these gene mutations also have an increased risk of breast cancer and prostate cancer.
Not all families with multiple cases of breast and ovarian cancer have mutations in BRCA1 or BRCA2.

How Common Is Hereditary Breast And Ovarian Cancer?

Like other gene mutations, BRCA1/2 mutations are rare in the general population. Women in the general population have about an 8% chance of getting breast cancer by age 70 and about a 12% chance by age 85.
This means in a group of 100 women without a mutation, about eight will get breast cancer by age 70 and about 12 by age 85.

Current estimates are less than 1% of the general population has a BRCA1/2 mutation.

Women who have a BRCA1/2 gene mutation have an increased risk of breast cancer. About 10-15% of women diagnosed with breast cancer have a BRCA1/2 mutation.

- BRCA1 carriers have a 55 to 65% chance of developing breast cancer by age 70.
- BRCA2 carriers have about a 45% chance of developing breast cancer by age 70.

This means in a group of 100 women with a BRCA1/2 mutation, between 45 and 65 will get breast cancer by age 70. These numbers represent average risk, so the risk of breast cancer for any one woman with a BRCA1/2 mutation may fall outside this range.

BRCA1/2 mutation is present in 10-30% of women under age 60 diagnosed with triple negative breast cancer. Together, BRCA1/2 mutations are thought to explain a large portion of hereditary breast cancers. Most breast and ovarian cancers, however, are not hereditary.

BRCA1 And BRCA2 Gene Mutations And Ethnicity

Among Ashkenazi Jewish men and women, about one in 40 have a BRCA1/2 mutation.

Approximately 1 in 10 women with breast cancer and 1 in 3 women with ovarian cancer in Ashkenazi families have BRCA1/2 mutations.

The table below shows how the prevalence of BRCA1/2 mutations varies among breast cancer survivors from different ethnic groups in alphabetical order.

Ethnicity	**BRCA1**	**BRCA2**
African-American	1%	3%
Ashkenazi Jewish	8-10%	1%
Asian-American	Less than 1%	Data not available
Caucasian (non-Ashkenazi Jewish)	2-3%	2%
Hispanic	4%	Data not available

BRCA1/2 Mutations And Ovarian Cancer

BRCA1/2 mutations increase a woman's risk of ovarian cancer.

For women in the general population, the lifetime risk of ovarian cancer is less than 2%.

However, for women with the BRCA1 mutation, lifetime risk of ovarian cancer up to age 70 is 35 to 70%.

For women with the BRCA2 mutation, this risk is 10 to 30%.

Factors That Increase Inherited Risk For Cancer

Many people are unaware of their inherited risk, though they may be aware of a cancer history in their family. You should consider talking with a doctor about genetic testing for hereditary breast and ovarian cancer (HBOC) syndrome if at least one of the following applies to you or your family:

- Breast cancer before age 50
- One or more relatives diagnosed at age 45 or younger
- Two or more relatives who've had breast cancer
- A male relative who's had breast cancer
- Breast cancer in both breasts or twice in the same breast
- Being in a family Ashkenazi or Eastern European Jewish ancestry
- Ovarian cancer at any age
- A family member with a BRCA1/2 mutation or mutations in other related breast cancer risk genes
- A history of breast cancer, ovarian cancer, prostate and/or pancreatic cancer on the same side of the family

BRCA1/2 Mutations And Cancer In Men

Men can also have BRCA1/2 mutations and may pass them on to their children.

Breast Cancer

Men who have a BRCA2 mutation have an increased risk of breast cancer.

In women 5 to 10% of breast cancers are considered to be due to gene mutations. However, in men up to 40% of breast cancers may be related to BRCA2 mutations. This means that men who get breast cancer are more likely to have an inherited gene mutation than women who get breast cancer.

In men, the lifetime risk of breast cancer is 1 in 1,000 for non-carriers and about 65 in 1,000 for BRCA2 carriers.

Men who have a BRCA1 mutation may also have an increased risk of breast cancer, but this link is less clear.

Prostate Cancer

Men who have a BRCA2 mutation may also have an increased risk of prostate cancer. For BRCA2 carriers, the lifetime risk of prostate cancer up to age 65 is about 15 to 20%.

Cancer Risks For Women With BRCA1/2 Mutation

- Lifetime risk of breast cancer: 50% to 85%
- Risk of breast cancer before age 50: 30% to 50%
- Lifetime risk of ovarian cancer:
  - BRCA1 gene mutation: 25% to 50%
  - BRCA2 gene mutation: 15% to 30%
- Developing a second breast cancer: 40% to 60%. The risk of breast cancer occurring in the other breast rises approximately 2% to 3% per year.

Cancer Risks For Men With BRCA1/2 Mutation

- Lifetime risk of breast cancer
  - BRCA1 gene mutation: 1% to 2%. This is a 10-fold increase over the general population.
  - BRCA2 gene mutation: 6%

- Risk of prostate cancer
  - BRCA1 gene mutation: some increased risk.
  - BRCA2 gene mutation: 20%

- Men with a BRCA2 gene mutation have a significantly increased risk of developing more aggressive prostate cancer before age 65 and therefore screening should begin at age 40.

About 5 To 10 Percent Of Colorectal Cancers Are Caused By An Inherited Mutation

Types Of Common Hereditary Colon Cancer

1. **Lynch Syndrome,** also known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC) is the most common hereditary cause of colorectal cancer and accounts for 2-3% of all colorectal cancers. The majority of Lynch syndrome is due to mutations in the MLH1, MSH2, MSH6, PMS2, or EPCAM (also known as TACSTD1) genes.

These mutations are associated with an increased lifetime risk for colorectal cancer (CRC) and other malignancies within the tumor spectrum including at least endometrial, ovarian, gastric, small bowel, urothelial, hepatobiliary tract, sebaceous and pancreatic cancers. These mutations can be inherited from a person's mother or father.

Lynch Syndrome affects 28,000 individuals annually. Cancer risks associated with Lynch Syndrome are largely derived from family studies. Mutations in MLH1 and MSH2 account for 70-90% of families with Lynch Syndrome.

Cancer Risks for Lynch Syndrome Mutation Carriers

Lynch Syndrome	Mutation Carrier Risk	General Population Risk
Colorectal	Up to 82%	2%
Endometrial (uterine)	Up to 71%	1.5%
Stomach	Up to 13%	< 1%
Ovarian	Up to 12%	< 1%
Second caner within 10 years	30%	3.5%
Second cancer within 15 years	50%	5%

2. **Familial Adenomatous Polyposis (FAP) or Attenuated FAP (AFAP)** which accounts for <1% of colorectal malignancies is an inherited condition that is caused by a mutation in the APC gene. Patients who have a mutation in the APC gene can have:

- Many precancerous polyps or adenomas; possibly hundreds or thousands in the colon and rectum.
- A milder form of FAP may present with a smaller number of colorectal polyps or adenomas.
- A greatly increased risk of colorectal cancer.
- An increased risk for other associated cancers.

An APC mutation can be inherited either from a person's mother or father.

Cancer Risks for FAP or AFAP; APC Mutation Carriers

FAP and AFAP	Gene Mutation Carrier Risk	General Population Risk
Colorectal cancer in FAP	Approximately 100%	2%
Colorectal cancer in AFAP	80-100%	2%
Small bowel cancer	5-12%	N/A

3. **MYH-Associated Polyposis (MAP)** is a syndrome that was discovered fairly recently and is rare. Because of the numerous colorectal polyps or adenomas that occur in MAP, the colorectal cancer risk is known to be significantly increased.

   Additionally, it is possible that risks of other cancers, such as small bowel, may be increased as well. Individuals with MAP often do not have a family history of colon cancer or colon polyps in family members, although siblings may be affected.

   MAP is caused by mutations in the MYH gene and individuals with MAP have mutations in both of their MYH genes, one from each parent.

Otogenetics Cancer Screening Panels

- **BRCA1/2 – 2 genes**

- **Breast and Ovarian Cancer – 15 genes**
  ATM, BRCA1, BRCA2, BRIP1, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, RAD51C, RET, STK11, TP53, VHL

- **Colorectal, Endometrial and Ovarian Cancer Panel - 12 genes**
  APC, BMPR1A, CDH1, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, SMAD4, STK11

- **Comprehensive Inherited Cancer Panel – 39 genes linked to Breast, Ovarian, Endometrial, Colorectal, Lynch Syndrome, Gastric, Melanoma, Pancreatic, Polyposis, Prostate, Renal, Thyroid/Parathyroid, Uterine and other major cancers** APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKn2A, CHEK2, ELAC2, EPCAM, FANCC, HRAS1, MEN1, MET, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, NTRK1, PALB2, PALLD, PMS2, PTCH, PTEN, RAD50, RAD51, RAD51C, RAD51D, RET, SMAD4, STK11, TP53, VHL

- **Lynch Syndrome - 5 genes** EPCAM, MLH1, MSH2, MSH6, PMS2

Mutations in each gene may be rare when evaluated individually, however they collectively account for a significant amount of hereditary cancer susceptibility. This panel may be appropriate in a number of scenarios, particularly if the family history shares features of several different hereditary cancer syndromes with multiple cancer types.

Screening For Hereditary Cancer Gene Mutations

The hereditary cancer gene test is most often a saliva or buccal (cheek) swab or blood test. Your test sample is collected in your doctor's office and sent to the laboratory for DNA analysis.

It takes 2-4 weeks before test results are available. Your doctor or genetic counselor will contact you with your test results, discuss their implications and go over your options. From a genetic screening test, you learn whether you carry an inherited cancer gene mutation and receive an estimate of your personal risk of inherited cancer.

Federal and state laws help ensure the privacy of your genetic information and protect against discrimination in health insurance and employment. In 2008, a federal law called the Genetic Information Non-Discrimination Act (GINA) was passed. Under the terms of GINA, medical insurance companies and employers are prohibited from discriminating against individuals on the basis of genetic information. GINA defines genetic information as including not only genetic test results, but also family cancer history, and the fact that genetic testing occurred.

Risks And Benefits Of Genetic Screening

The medical risks from having blood drawn for a genetic test are very small and are associated with having your blood drawn such as lightheadedness, bleeding or bruising. Saliva or buccal samples do not carry these risks. Test results however, may have an effect on your emotions, social relationships, finances, and medical choices. If you test positive for gene mutation associated with a hereditary cancer, you may feel anxious, depressed, or angry. You will have to make difficult decisions about whether or not to take steps to lessen your risk of developing cancer and about what follow up care is right for you. You may also have feelings of "inevitability" that you'll get cancer.

If you test negative for having a gene mutation associated with hereditary cancer, you may experience survivor guilt caused by the knowledge that you likely do not have an increased risk of developing a disease that may have affected your loved ones.

Because there are instances when a test result may be ambiguous, meaning that you have a genetic mutation which has not been associated with cancer in other people, you may feel uncertainty and concern that your result may not be a true negative result.

What Do My Test Results Mean?

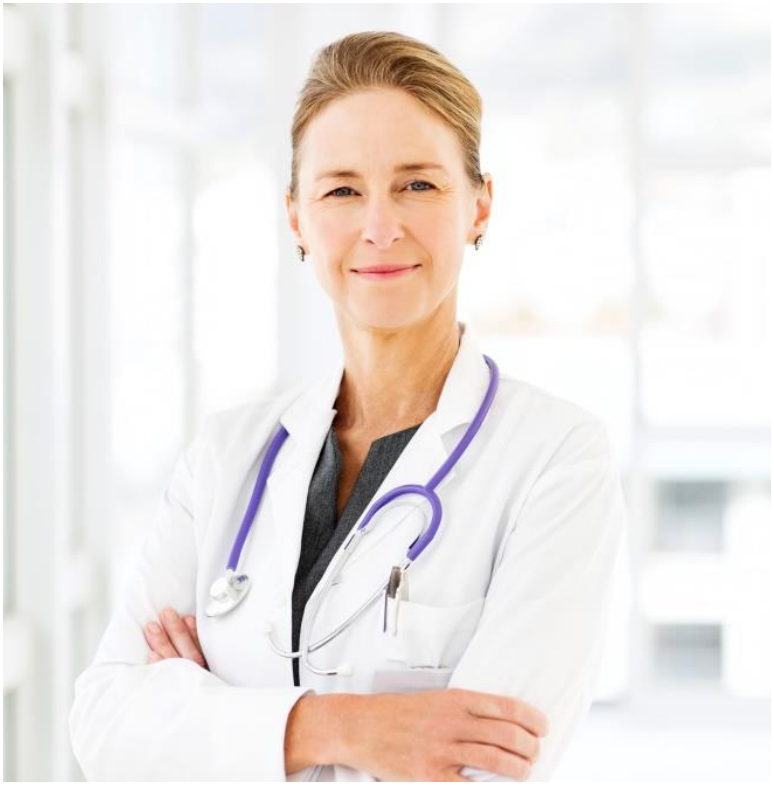
Testing does not tell you if you currently have cancer. Your test results tell you about your inherited ***risk*** of having breast and ovarian or other types of cancer.

A **negative** test result means that you do not have a gene mutation in the genes that were evaluated in the Gene Panel Testing.
Although the gene test can detect the majority of mutations:

- You could have a gene mutation that the test wasn't able to detect.
- Or if your family carries a high-risk gene mutation that researchers haven't yet identified then the test would not be able to detect this gene mutation and you could be a carrier.

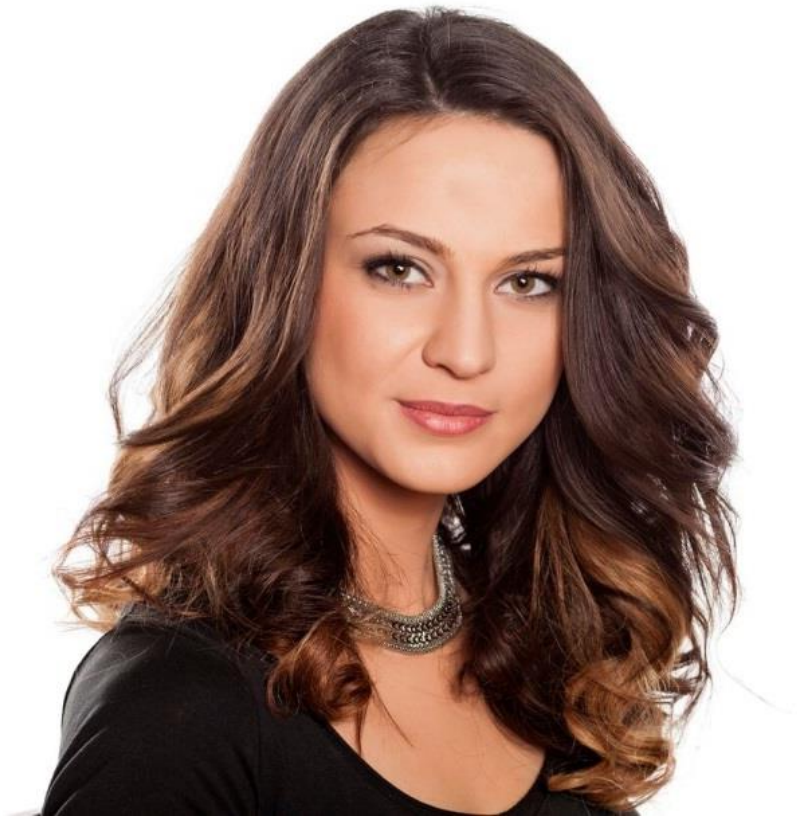
A negative test result does not eliminate the chance of developing a non-hereditary cancer. You still have the same cancer risk as that of the general population.

A **positive** test result means that you have a gene mutation that is associated with cancer. A positive test result does not mean that you have cancer or that you will have cancer. For example, having the BRCA1/2 mutations does not mean that you will get breast cancer. Many women with a BRCA1/2 mutation will never have breast cancer. A positive test result tells you that you have a much higher risk of developing cancer compared with someone who does not have the mutation.



A positive test result helps you to better understand your personal risk of developing cancer. You can then make choices on what to do to reduce your risk and about what follow up care is right for you.

Sometimes, **variant(s) of unknown significance (VUS)** is included in the report. VUS are variants that do not fit into positive or negative classifications according to relevant Professional standards.



Should I Talk With My Relatives About My Result?

You are encouraged to share these results with your relatives. It is normal to feel some anxiety about this. But knowing this information may help your relatives understand their own future risk of developing cancer, which may help them prevent a cancer or detect it early. However, keep in mind that not everyone wants to know their cancer genetic status and genetic testing is a personal decision. Talking about genetic test results and their impact on the family is an ongoing discussion rather than a one-time conversation.

Who Specifically In My Family Should Also Get Tested?

Mutations in the certain genes are inherited in a dominant fashion. This means that each of your siblings and children has a 50% chance of having inherited the same mutation. This mutation was likely inherited from one of your parents. If they choose to undergo testing, this can determine which side of your extended family is also at risk to have the same mutation(s).

It is typically recommended that an individual undergo genetic testing at an age at which it will impact their medical care. In children <18 years, genetic testing is generally not recommended when results would not impact medical management.

Your healthcare provider may arrange for you to meet with a genetic counselor to discuss your test results and how they may affect your family.

Follow-Up Care After A Positive Test Result

You might choose to take specific measures to reduce your cancer risk. What you choose to do depends on many factors, including your age, medical history, prior treatments, past surgeries and personal preferences.

To reduce your cancer risk after a positive test result, you might:

Increased Screening: Having clinical breast exams every six months and mammograms and magnetic resonance imaging (MRI) exams every year may be recommended. Each type of hereditary colorectal cancer calls for a different management strategy, but frequent monitoring is often the primary approach.

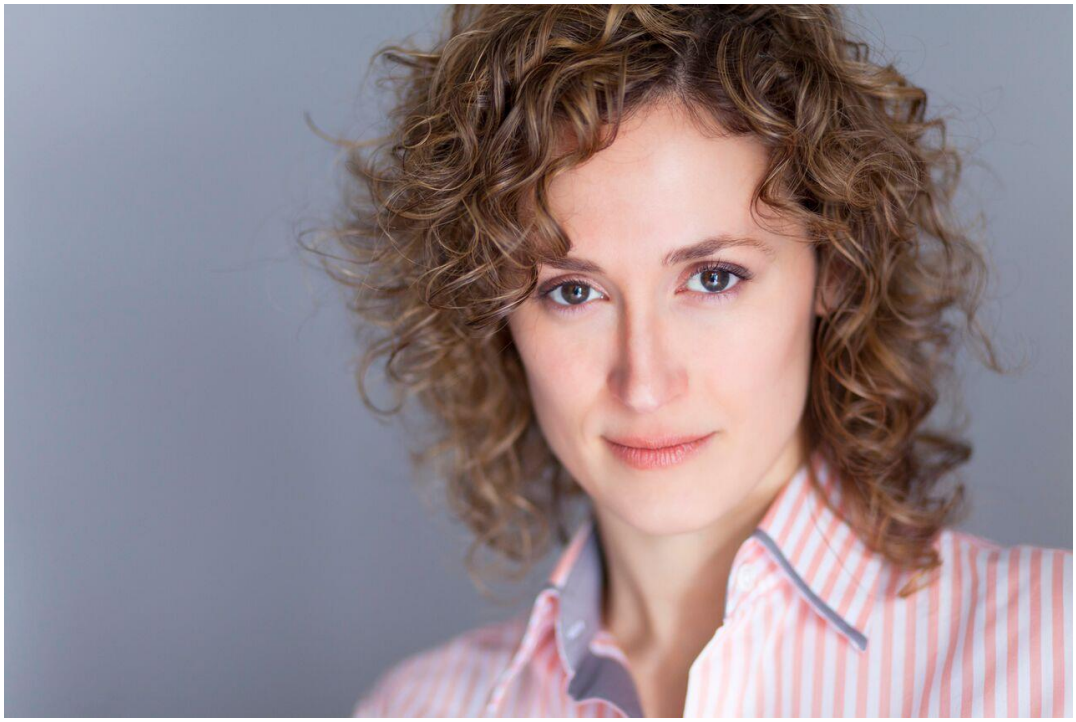
Use of Oral Contraceptives: Oral contraceptive use has been shown to reduce ovarian cancer risk in BRCA mutation carriers. However, risk of breast cancer goes up slightly with oral contraceptive use for more than five years.

Chemoprevention: Take a medication to reduce your risk of cancer. Medications may be used to reduce the number of polyps that remains after colon surgery, while monitoring for signs of cancer.

Undergo Preventive Surgery:

- **Preventive (Prophylactic) Mastectomy:** For persons with the BRCA gene mutations, removal of healthy breast tissue reduces breast cancer risk by about 90%.
- **Preventive Salpingo-Oophorectomy:** In premenopausal women, removal of healthy fallopian tubes and ovaries reduces breast cancer risk by as much as 50%. In both pre and postmenopausal women, it also reduces ovarian cancer risk by as much as 90%.
- **Removal of the colon** is often recommended depending on the number of polyps or in patients who develop colon cancer. The rectum is usually left in place.
- **Preventive removal of the uterus (endometrium) and/or ovaries** reduces the risk of uterine and/or ovarian cancer and may be an option when childbearing is complete.

Preventive surgery does not eliminate all cancer risk. It is possible for cancer to develop in any tissue that couldn't be removed through surgery.



Patient Advocacy

FORCE
Facing Our Risk of Cancer Empowered
www.facingourrisk.org

We Can
Women's Empowerment Cancer Network
www.womenscanceradvocacy.net

Susan G, Komen
http://ww5.komen.org

Gynecologic Cancers Foundation
www.thegcf.org

Patient Advocate Foundation
www.patientadvocate.org

The Pink Gene Foundation
www.pinkgenefoundation.org

Share 40
For Women Facing Breast and Ovarian Cancer
www.sharecancersupport.org

American Cancer Society
http://www.cancer.org

Fight Colorectal Cancer
http://www.globalcoloncancer.com

Men Against Breast Cancer
Caring About The Women We Love
http://www.menagainstbreastcancer.org

Young Survival Coalition
Young Women Facing Breast Cancer Together
https://www.youngsurvival.org

Breast Cancer Trials
https://www.breastcancertrials.org

Living Beyond Breast Cancer, With You For You
http://www.lbbc.org

National Ovarian Cancer Coalition
http://www.ovarian.org

Male Breast Cancer Coalition
www.malebreastcancercoalition.org

abcd-After Breast Cancer Diagnosis
power of one-to-one
http://www.afterbreastcancerdiagnosis.com

NIH-National Cancer Institute
http://www.cancer.gov

Lynch Syndrome International
www.lynchcancers.org

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