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SHARING OUR METASTATIC BREAST CANCER STORY

Understanding Biomarker and Genetic Testing in Metastatic Breast Cancer (MBC) Care

Biomarker and genetic testing often get tossed around in the world of cancer. While they both play an important role in your treatment journey, the two forms of testing are very different. This guide serves to define biomarker and genetic testing, explain how each fit into your diagnostic and treatment decisions, and how to communicate this important information to your loved ones.

Biomarker Testing

What is Biomarker Testing?

Just as each patient has a unique personality, so does each tumor. Some tumors are driven by the presence of unique sets of alterations, often called biomarkers. It may be helpful to think of a "biomarker" like the "thumbprint" of a tumor, and this thumbprint may be measured or convey certain aspects of your tumor that can help guide your treatment options. When doctors identify the specific thumbprint of a tumor – its pattern of biomarkers – through biomarker testing, they can often prescribe medicines that are designed to target those specific traits.

Biomarker testing is different from genetic testing, which is used to look at the genes inherited from a person's parents to find out one's lifetime risk of developing certain cancers. It's important to note that a genetic alteration can be hereditary (passed down from a parent) or acquired (developed later in life through certain environmental risk factors).

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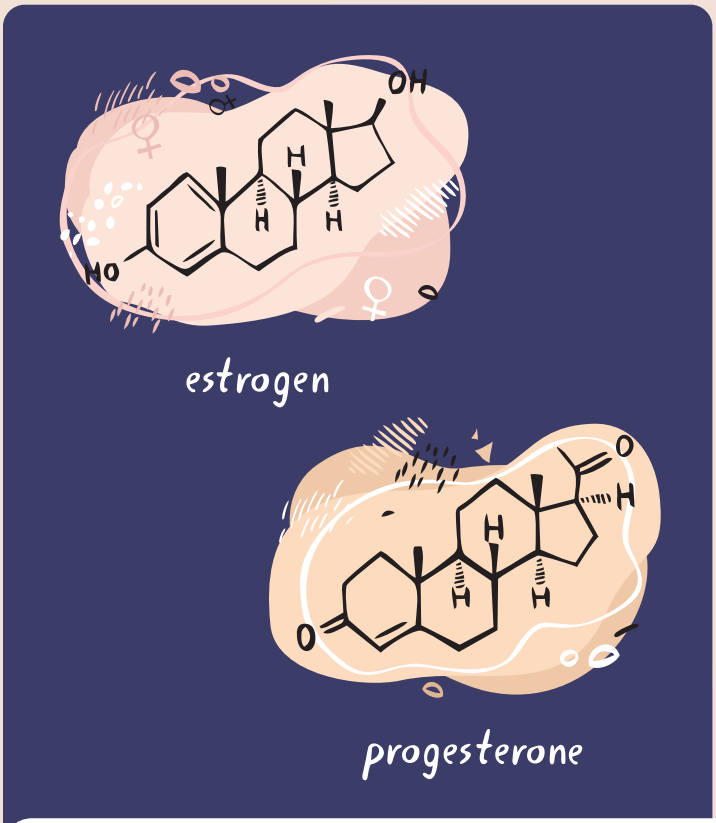
Possible MBC Types

Biomarker testing can help determine which type of MBC you have to help your doctor make informed treatment decisions. The following is an overview of the most common current MBC types:

- Estrogen receptor positive (ER+)
- Estrogen receptor negative (ER-)
- Progesterone receptor positive (PR+)
- Progesterone receptor negative (PR-)
- Human epidermal growth factor receptor 2 positive (HER2+)
- Human epidermal growth factor receptor 2 negative (HER2-)
- Triple negative (TN)



How Can Hormones Influence MBC

Breast cancer can be hormone driven and the progression of the disease can be directly related to the types of hormones present.

Approximately two-thirds (60-70%) of MBC patients have breast cancers that are hormone receptor (HR) positive, meaning their growth is fueled by either estrogen or progesterone. Some breast cancer cells contain proteins that act as estrogen or progesterone receptors. When estrogen or progesterone attach to these receptors, they drive cancer growth. Cancers are called HR-positive or HR-negative based on whether or not they have these receptors.

If your doctor tells you that you are ER- or PR-, that means your MBC is not driven by either of these proteins.

What are HER2 and Triple Negative?

HER2 (Human Epidermal Growth Factor Receptor 2) is a protein that acts as a receptor on the surface of a cancer cell. When there are too many HER2 proteins present, the cancer is considered to be HER2+. About 20% of cancers have too much of this protein and are considered HER2+.

Triple negative MBC occurs when the tumor tests negative for estrogen and progesterone and HER2 protein. In this case, cancer growth is not supported by hormones nor by the presence of too many HER2 proteins. About 15% of MBC is triple negative.

How is Biomarker Testing Done?

Biomarker testing is typically done by testing a tissue sample from your tumor after surgery or biopsy, or, in some cases, with a blood test.

What Can I Do with This Information?

Talk to your medical team to determine what your tumor's hormone receptor and HER2 status means for your MBC treatment journey. Knowing your tumor's hormone receptor and HER2 status are critical for working with your doctor to help inform treatment options for your cancer.

It may be necessary to recheck the biomarker status of the tumor periodically because it could change over time. Also, testing the areas where the tumor has spread for ER, PR, and HER2 may be recommended, because the status of these receptors on a tumor can potentially change once it has spread. It's important to know of any change in status for any new areas of tumor metastasis to help your doctor learn more about the tumor and determine the appropriate treatment plan. However, HR and HER2 status are just one factor your doctor will consider when deciding on treatment options; others include your overall health, the extent to which the cancer has spread, location of the cancer and any previous treatments you've had.

Based on your biomarker testing results you can also discuss with your medical team clinical trials that you may be able to participate in.

Questions to Ask Your Doctor

To help you learn more about biomarker testing for MBC and how the results may inform treatment options, consider asking your doctor the following questions:

- Which biomarker tests do you recommend, and why?
- How will the biomarker tests be performed?
- How often do I need these tests?
- What do the results mean?
- What does it mean if my hormone receptor and HER2 status of new tumors differ from the results of the original tumor?
- How will the results inform my treatment options?

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Understanding MBC and the Genetic Connection

Other types of MBC are classified according to the presence of an alteration in genes or a specific trait in the tumor cells. Gene alterations can be hereditary (passed down from a parent) or acquired (developed later in life through certain environmental risk factors). Knowing which type of gene alteration you have, which can be determined with advanced genomic testing, can help your doctor make informed treatment decisions. Genetic alterations that may be present in MBC tumors include:

Alteration Type	Inherited	Acquired
BRCA1 and BRCA2	X	X
EGFR		X
ATM	X	X
BARD1	X	X
CHEK2	X	X
PALB2	X	X
STK11	X	X
PIK3CA		X
mTOR		X
TP53		X
AKT1	X	X
PTEN	X	X
CDHI	X	X
APC		X
NRAS		X
KRAS		X
CDK4		X

BRCA1 and *BRCA2*

Breast cancer susceptibility genes 1/2 are human genes that produce proteins responsible for repairing damaged DNA and play an important role in maintaining the genetic stability of cells. While everyone will inherit copies of these genes, an alteration on this gene, either hereditary or acquired, can lead to increased risk of cancer.

BRCA gene alterations can be either hereditary (also called germline), meaning you are born with them and they were passed on from your mother or father, or acquired later in life (called somatic alterations).

Alterations in the following genes have also been linked to breast cancer:

EGFR

The epidermal growth factor receptor (EGFR) is a protein that lives on the surface of normal cells and cancer cells. An alteration in the *EGFR* gene is acquired and can drive abnormal cell growth, which can lead to cancer. **Approximately half of all triple-negative breast cancers** have cancer cells that make too much *EGFR*.

BARD1

An alteration in one copy of *BARD1* gene **increases the risk of female breast cancer**, including triple-negative breast cancer, as well as other types of cancers such as ovarian cancer.

CDK4

Cyclin Dependent Kinase 4 is a protein coding gene, mediates progression through the G1 phase when the cell prepares to initiate DNA synthesis. ***CDK4* is altered in 1.21% of breast carcinoma patients**.

PIK3CA

PIK3CA is a gene that encodes a lipid kinase involved in multiple signaling pathways. These pathways influence cellular functions such as growth, death, and proliferation. **Acquired alterations in this gene are found in 30-40% of all breast cancers**.

APC

The *APC* gene instructs the body in making the APC protein, which acts as a tumor suppressor by keeping cells from growing and dividing too quickly. Alterations in this gene can **lead to breast cancer**.

KRAS

Another type of oncogene that instructs the body to make a protein called K-Ras, which tells cells to grow and divide. **Less than 2% of breast cancers have a *KRAS* alteration**.

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ATM

Instead of activating DNA repair, the defective ATM protein allows alterations to accumulate in other genes, which may cause cells to grow and divide in an uncontrolled way. This kind of unregulated cell growth can lead to the formation of cancerous tumors. Inheriting one abnormal copy of this gene has been linked to a high rate of breast cancer. It has been suggested that women who carry an alteration in the *ATM* gene have an **estimated 20-60% increased risk for breast cancer**. Those with an *ATM* gene mutation are thought to be at increased risk for early-onset breast cancer and bilateral breast cancer.

PALB2

The *PALB2* gene is called the partner and localizer of the *BRCA2* gene. It provides instructions to make a protein that works with the BRCA2 protein to repair damaged DNA and stop tumor growth. Alterations in the *PALB2* gene are known to carry a predisposition to developing breast cancer. **The estimated lifetime risk is between 33 and 58%**.

CHEK2

CHEK2 is a tumor-suppressor gene that protects cells from becoming cancerous. People who inherit alterations in the gene are at an increased risk for certain types of cancer, thus **risk of developing breast cancer can be increased by 37%**.

PTEN

The *PTEN* gene helps stop the growth of tumors. It's known as a tumor suppressor. A tumor suppressor gene is like the brakes on a car. It puts the "brakes" on cells, so they don't divide too quickly. Mutations in one copy of the *PTEN* gene can **increase the chance for developing certain types of cancer** in one's lifetime, including breast cancer.

TP53

(also known as *p53*): An alteration in this gene, which helps stop the growth of cells with damaged DNA, is a **rare cause of breast cancer**.

STK11

The *STK11* gene (also called *LKB1*) provides instructions for making an enzyme called serine/threonine kinase 11. This enzyme is a tumor suppressor, which means that it helps keep cells from growing and dividing too fast or in an uncontrolled way. People with an inherited alteration in *STK11* gene are at a **greater lifetime risk of developing many different types of cancer**, including breast, ovarian, endometrial, cervical, pancreatic, colorectal, gastric, small intestine, and lung cancer. The lifetime risk for a woman with an *STK11* mutation is about 32-54% compared to 12.5% for an average-risk woman.

AKT1

This gene provides instructions for the body to make a protein called AKT1 kinase, which is found in cells throughout the body. It helps **regulate cell growth, division and survival, and also the process by which cells self-destruct when they become damaged**. The *AKT1* gene alteration is seen in cancers including breast, colon and lung.

mTOR

A protein found on various types of cells throughout the body, which is produced as a result of instructions from the *mTOR* gene. **When *mTOR* is overactivated due to a genetic alteration, cancer may result**.

NRAS

The *NRAS* gene instructs the body to make a protein called N-Ras that is involved in regulating cell division. *NRAS* belongs to a class of genes called oncogenes that, when altered, **can cause normal cells to become cancerous**.

CDHI

Women with an alteration in this gene have an **increased risk of invasive lobular breast cancer**.

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Understanding MBC and BRCA

BRCA1 and *BRCA2* genes (BReast CAncer susceptibility genes 1 and 2) play a role in protecting the body against certain cancerous cells. Everyone has these genes, but some people are born with an alteration to this gene, or can acquire an alteration later in life. People with *BRCA* alterations are more likely to develop cancers such as ovarian and breast cancers – including MBC. A simple blood, saliva or tissue test can determine if you have the alteration and can be administered/recommended by a healthcare professional.

What are *BRCA1* and *BRCA2* Genes?

An alteration in one or both *BRCA1* and *BRCA2* genes increases the risk of breast and other cancers. *BRCA* gene alterations can be either hereditary or acquired later in life. About **55%-72% of women** who inherit a harmful *BRCA1* variant and **45%-69% of women** who inherit a harmful *BRCA2* variant will develop breast cancer by 70-80 years of age.

How Can *BRCA1* and *BRCA2* Alterations Influence Breast Cancer?

Women who have *BRCA1* or *BRCA2* alteration have a:

- 45-75% risk of developing breast cancer at any stage in their lifetime — about 3 to 7 times greater than women who don't have the alteration
- Tendency to develop breast cancer at a younger age (45 and under)
- Greater likelihood of developing cancer in both breasts

At this time, it is unknown if *BRCA1* or *BRCA2* influence progression of the disease.

Who is Most at Risk for a Genetic Alteration?

You are more likely to have an inherited alteration if you, or a blood relative on either side of the family have had:

- Breast cancer before the age of 50
- Cancer in both breasts
- Both breast and ovarian cancers on the same side of the family or in a single individual
- Multiple breast cancers
- Two or more types of *BRCA1*- or *BRCA2*-related cancers (breast, ovarian, pancreatic, prostate, melanoma) are in a single family member
- Triple-negative breast cancer
- Pancreatic cancer
- Male breast cancer in the family
- Prostate cancer at age 55 or younger or metastatic prostate cancer at any age

While some ethnicities — for example people of Ashkenazi Jewish descent — are at increased risk of genetic alterations, they are found in people in every ethnicity.

What Can I Do If I'm at An Increased Risk for a Genetic Alteration?

Your doctor may recommend talking to a genetic counselor about taking a genetic test. Genetic testing is usually performed using blood, saliva or a tissue sample. A *BRCA* gene test does not test for cancer itself. The sample is sent to a laboratory and takes several weeks for results. Test results can be positive, negative or inconclusive. Knowing your *BRCA* status may affect medical options for cancer treatment or prevention for you and your relatives.

Are There Resources That Can Help Me Decide If I Should Have a Genetic Test?

Talking to a genetic counselor is generally recommended before and after having a genetic test. Counseling usually covers many aspects of the testing process, including a hereditary cancer risk assessment based on an individual's personal and family medical history. Discussion topics may include:

- Is genetic testing appropriate for me?
- Which genes to test for and which tests to order?
- Interpretation of test results and what it means for you and your relatives
- Psychological risks and benefits of genetic test results
- Is the genetic test covered by insurance?

Talk with Your Loved Ones About Your Genetic Test

If you have a *BRCA* alteration, you have a 50% chance of passing it on to your children and there is a 50% chance your siblings have the alteration. Therefore, the results of your genetic test can impact medical decisions and options for you and your family, so it's important to share your results with loved ones.

Telling Your Loved Ones

- Sharing genetic test results with your family isn't easy. Your test results may raise concerns among family members about their own cancer risk and medical decisions
- Hereditary cancer risk can affect individuals in different ways and your relatives may react differently than you did to genetic testing. They may need additional information and emotional support
- Genetic counseling and testing could help your relatives gain a better understanding of their cancer risk. If they test positive, options for detecting and treating cancer are available. If they test negative, they will know they're not at an increased risk for developing a hereditary cancer
- A genetic counselor can advise you and your family on whether you should consider taking the test or how to deal with the results

Counseling May Include:

- Assessing risk
- Interpreting test results
- Identifying family members who may be candidates for testing
- Explaining medical options for cancer treatment and prevention based on your test

Dealing With Emotions

- It's not unusual to feel overwhelmed, anxious or fearful when telling your family about your *BRCA* alteration status. These are normal emotions, so don't be hard on yourself. Accept that you cannot control your family's reaction or their emotions – but remember how you felt when you first received your test results
- Consider sharing what you're going through with close friends or connect with others also affected by hereditary cancer through national advocacy and local support groups
- Remember to make time for yourself, limit alcohol, eat well-balanced meals and try to get enough sleep

Questions to Consider

- How will I react to my test results and what will I do if they are positive?
- Am I prepared to cope with the results?
- How will my result affect my family?
- Should my family know the results of the test?
- How will I talk to my children about my result?

Available Resources

Some family members may not want to learn more about hereditary cancer syndrome or get tested. But for those who do, a genetic counselor may be able to help you compile information to share with relatives, including helping them find a genetics expert in their area. Some advocacy groups also provide guides that can help you share test results with relatives.

- **FORCE:** A national nonprofit organization specializing in hereditary cancers, has a Peer Navigation Program that will match you with a trained volunteer and personalized resources: www.facingourrisk.org/get-support/PNP
- **Sharsheret:** A national not-for-profit organization supporting young Jewish women and their families facing breast cancer: www.sharsheret.org
- **Know:BRCA:** The Know:BRCA online tool, which is part of the Centers for Disease Control and Prevention's (CDC) Bring Your Brave program, is a resource developed to help patients understand their risks for having a *BRCA1* or *BRCA2* gene alteration: www.knowbrca.org

For more information, visit LifeBeyondPink.com