HOPE'S STORY

I was diagnosed with carcinoma of an unknown primary, a rare scenario in which malignant cancer cells are found in the body, but the place in the body where the cancer began is not known. Thus, it was imperative for me to undergo several tests to gather key information in order to determine the best treatment plan. A biopsy of the tumor in my lower back indicated that estrogen receptors were present in the cancer cells. With this in mind, my oncologist chose a combination of therapies: radiation treatment and an estrogen blocker. This was thought to be the best treatment plan given what was understood about the biologic features of my tumor.

Once the initial treatment was completed, my oncologist recommended an additional biomarker test. This test revealed that the cancer cells were positive for the *PIK3CA* and *PTEN* gene mutations. The doctor told me that these were mutations present in the tumor, but not something inherited from my parents or able to be passed to my children. My oncologist revised the combination of medicines prescribed to include a new drug, designed to reduce cancer growth in people whose tumors have *PIK3CA* and/or *PTEN* gene mutations.

Biomarker testing was crucial in my case. I am so grateful that the testing process was simple and pain free. I feel blessed to continue benefiting from medical advances that are prolonging my life.

IF YOU ARE AT RISK OF OR HAVE BEEN DIAGNOSED WITH BREAST CANCER OR OVARIAN CANCER AT ANY STAGE, WE CAN HELP.

Connect with others who share your experience with clinical trials through our national peer support network.

Discuss genetic concerns related to your family history and cancer risk with our genetic counselors and support staff.

Let us help you support your children through the cancer journey with parenting resources.

Create a survivorship plan tailored to your unique needs.

Learn how to address the cosmetic side effects of cancer treatment.

Join our group of women living with advanced breast cancer or recurrent ovarian cancer.

Call us for resources or with questions from family, caregivers, and friends.

Stay informed about clinical trials from experts in the cancer community through our national webinars and access transcripts from previous webinars on our website.

To find out more, call 866.474.2774, email info@sharsheret.org, or visit us at sharsheret.org.

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Sharsheret is a Jewish not-for-profit organization supporting women and families facing breast cancer and ovarian cancer.

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The Jewish Breast Cancer & Ovarian Cancer Community

BR_BM_C

Understanding Biomarkers: Your Path to a Tailored Treatment Plan

SHARSHERET

WHAT ARE BIOMARKERS?

Biomarkers are substances that show the potential or presence of disease. They may be proteins, genes, hormones, or genetic mutations and can be found in blood or other body fluids. Biomarkers are used to identify exactly what type of breast cancer you have, how quickly the cells might grow, and how likely it is to recur. They can help you and your doctor decide on the best treatments and monitor how well the cancer responds to medical intervention. Besides standard treatments, biomarkers may help determine if you might benefit from either experimental therapies or clinical trials.

There are many ways biomarkers can be described, including terms such as "genomic," "somatic," or "tumor profiling." Even the term "liquid biopsy" is used when discussing biomarkers.

BIOMARKER TESTING VS. HEREDITARY CANCER TESTING

Biomarker testing is different from hereditary genetic testing. Hereditary genetic testing looks for genetic changes that are passed down through families. This type of testing identifies mutations that may increase the risk of developing cancer. It must be done on non-cancerous cells, which can include blood, saliva, or skin.

Most biomarkers are only associated with cancer cells, although rarely, some hereditary gene mutations can serve as biomarkers as well. Since tumor cells come from normal cells, they carry the hereditary mutations that show up in both hereditary genetic testing and biomarker testing. For example, hereditary *BRCA1* and *BRCA2* mutations are present in normal cells and in tumor cells, which may mean that targeted treatment with PARP inhibitors is indicated.

WHAT BIOMARKER TESTING IS ASSOCIATED WITH THE INITIAL DIAGNOSIS OF BREAST CANCER?

Historically, biomarker testing has been done on all breast cancers. This testing is performed on either the breast biopsy or the tumor removed during surgery. It is usually an immunohistochemical test, which means that some tissue is exposed to a dye attached to an antibody that will bind with the substance being tested for. When the pathologist looks at the cells under the microscope, they can see if the cells contain the substance of interest.

Breast cancer pathologists primarily look for the presence of estrogen receptors (ER), progesterone receptors (PR), and a growth factor receptor called HER2, as well as measuring Ki-67, which indicates how quickly the cancer cells are dividing. Pathologists use a grading system based on how strongly the dye is colored, allowing them to determine how many of the receptors are present and how strong the signal is. Some biomarkers are reported as "percentage present," while others are reported in ranges such as "absent," "low," or "high" expression.

Depending on the biomarkers and signal strength, an individual may benefit from targeted treatments. If ER and/or PR are present, anti-estrogen hormonal treatment may be an option. If the expression of HER2 is high, treatment targeted to the HER2 receptor can be beneficial. There are various options available in treating tumors that are ER/PR positive or HER2 positive.

Tumors that lack all three of these biomarkers are called "triple negative." The absence of these biomarkers can itself be a biomarker, as triple negative breast cancer may be eligible for a specific treatment protocol.

ADDITIONAL BIOMARKER TESTING FOR SOME BREAST CANCERS

At the time of diagnosis, additional biomarker testing may be done to determine whether hormonal therapy and/or chemotherapy are beneficial. These tests check certain genomic changes in the tumor that give information about the prognosis and the possible benefits of additional treatment.

THERE ARE MANY OTHER BIOMARKERS THAT CAN HELP INFORM TREATMENT PLANS

PD-L1 is a checkpoint for the immune system that might be mutated in cancer cells. Checkpoint mutations allow the cancer to avoid being detected by the immune system. Targeted treatments called immunotherapy may reduce the cancer cells' ability to avoid immune detection.

ESR1 mutations, which occur in the estrogen receptor, allow the receptor to be activated in the absence of estrogen. The presence of *ESR1* mutations in cancer cells may indicate the use of medications that downgrade the receptor.

PIK3CA is part of a growth factor pathway that regulates when cells divide and grow. In breast cancer, a mutation in this process may cause it to get stuck in the "on" position. Targeted medications can help with this.

BRCA mutations can be inherited from a parent, but sometimes the mutation develops only in the tumor cells. If this is the case, medicines called PARP inhibitors may be recommended.

Tumor mutational burden is related to the number of mutations present in the cancer cells' genetic material. This is a marker that indicates if the tumor may be susceptible to immunotherapy, even without a *PD-L1* mutation.

Broad cancer biomarker testing may be indicated if the cancer has spread beyond the breast. There are tests that look at hundreds of mutations in the tumor, including mutations not usually seen in breast cancer that might have approved or experimental targeted treatment available.

Circulating tumor DNA, or ctDNA, looks in the bloodstream for pieces of DNA shed from the tumor. This might also be called a "liquid biopsy." This test might be done to detect the early presence of a cancer recurrence, to track treatment effectiveness or to detect mutations. It is not standard practice to use ctDNA for monitoring or treating breast cancer.

BIOMARKERS TESTING FOR OVARIAN CANCER

Biomarker testing is different depending on the type of ovarian cancer. Patients with ovarian cancer should undergo both hereditary (germline) testing of their DNA and biomarker testing of the tumor. Biomarker testing means that the tumor DNA is sequenced to give your doctor specific information about possible mutations in the tumor.

For ovarian cancer, hereditary *BRCA1* and *BRCA2* mutations can be crucial in determining treatment. It is recommended that all patients with epithelial ovarian cancer undergo testing to determine if *BRCA1* and *BRCA2* mutations are present in their DNA and the DNA specific to the tumor. Their presence may suggest a benefit to treatment with a PARP inhibitor.

Another important tumor test for ovarian cancer looks for homologous recombination deficiency (HRD). An HRD score may show that the tumor is having trouble repairing its DNA, which can also benefit from PARP inhibitors.

CA-125 and HE-4 (human epididymis 4) are both proteins that may be elevated in the setting of epithelial ovarian cancer. This protein will be followed throughout treatment and in surveillance, if elevated at the time of diagnosis. For patients with other forms of ovarian cancer, other proteins that may be checked include inhibin A, inhibin B, AFP (alpha fetoprotein), HCG (human chorionic gonadotropin), and LDH (lactate dehydrogenase).

Another biomarker is microsatellite instability, or MSI. This may also be referred to as mismatch repair deficiency (MMR-D). MSI is common in Lynch syndrome, a pattern of hereditary cancer that includes colon, endometrial, and ovarian cancer, among others. If MSI is high, it may indicate that immunotherapy drugs could be useful.

Folate receptor alpha (FR-alpha or *FOLR1*) is also an immunohistochemical biomarker that can be checked in ovarian cancer and is associated with several targeted treatments.

Other biomarkers can play a role in ovarian cancer. These include tumors that overexpress HER2, have a *RET* gene fusion, or an *NTKR* fusion. Broad cancer biomarker testing may be indicated if the cancer has spread beyond the pelvis to help identify if there are any other mutations not usually seen in ovarian cancer that might have approved or experimental targeted treatment.

DOES BIOMARKER TESTING CHANGE WHEN THERE IS A RECURRENCE OF CANCER?

If cancer comes back, especially at a more advanced stage, it is important to biopsy and recheck the biomarkers. Tumors evolve, and a new mutation that happens by chance can give cancer cells an advantage. These can soon outnumber previous cells that were slowed down by prior treatment.

Some cancers that are initially designated as HER2 negative may actually later become HER2 low or high. This means that the amount of HER2 expressed might be too low to benefit from a targeted medication at the beginning of treatment but may be high enough to qualify after recurrence.

HOW DO I FIND OUT IF I SHOULD HAVE BIOMARKER TESTING DONE, OR REDONE?

It is important to discuss biomarkers with your oncologist. Testing of the tumor can identify important targets that might be driving cancer growth. Matching your medications to specific features of the tumor can potentially make a big difference to treatment outcomes.