Patient Advocate Foundation

Getting the Right Test at the Right Time

A CANCER PATIENT'S GUIDE TO BIOMARKERS

Personalized Medicine – A New Approach to Cancer Treatments

There is a reason why coffee shops offer a variety of options, everyone likes different things, and they are in business to satisfy individual taste. This has not always been true when a patient was diagnosed with cancer. Based on the type of cancer, the patient often received the same medical treatment as others with the same cancer. Times are changing and there is an emerging field of medicine where remarkable progress is being made, referred to as personalized medicine. Based on advances in this field, new treatments and testing are changing the "one-size-fits-all" approach and providing more choices.

Researchers will continue to investigate treatment options, using information that is unique to your cancer to provide you with the best treatment options. Additional information on some of the newest treatment options can be found on the websites of cancer-specific organizations and by discussions with your medical team.

This guide will focus on the basics of cancer biomarkers along with tips on the practical aspects such as access. Patient Advocate Foundation remains committed to helping you address any financial or insurance barriers you face with gaining access.

Call us any time at **800-532-5274** or visit **www.patientadvocate.org** for help!

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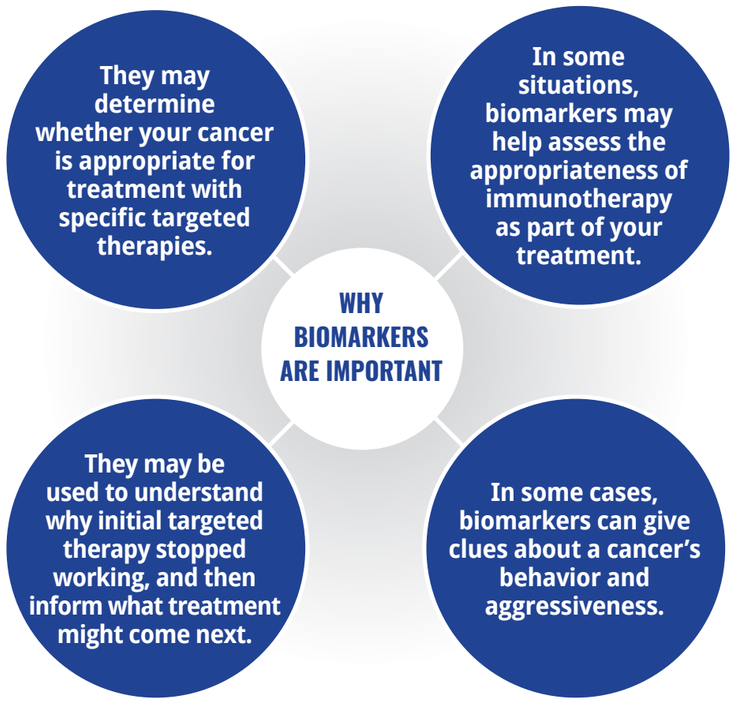
The information being discussed is specific to changes in cancer cells unrelated to family history or inherited risk.

What is a Biomarker?

Biomarkers, which can include changes in cancer DNA or the measurement of certain cancer proteins, can provide useful information about the cancer itself: how it might behave or how it might be treated.



Biomarkers are making healthcare more precise and cost-effective resulting in improved health outcomes and are often used when determining eligibility for clinical trials to evaluate targeted drugs and immunotherapy based on specific characteristics.

Case Study

John Smith is a 72-year-old man. He had a 2-month history of lower abdominal pain, weight loss and bloody diarrhea. His colonoscopy identified a mass in his colon which was biopsied. He also had a Chest, Abdominal and Pelvic CT scan. He had surgery to remove the tumor in the colon and was diagnosed with stage 4 colon cancer with metastases to the lung. After undergoing next generation sequencing his results showed a BRAF V600E mutation and a MSI-H tumor. His doctor recommended he begin immunotherapy.

COLORECTAL CANCER BIOMARKER MUTATIONS

- KRAS
- RAS
- BRAF V600E
- MSI-H
- dMMR

Key Vocabulary & Terms

Biomarker: a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. Also called molecular marker and signature molecule.

Biomarker testing (mutation, genomic or molecular testing): the analysis of a patient's tissue and/or blood for specific driver mutations, multiple gene alterations, and/or non-genomic biomarkers, with no relation to anything inherited within a family.

Biopsy: the removal of cells or tissues for examination by a pathologist.

Cancer biomarker: produced by the tumor itself, or may be a specific response by the body to the presence of cancer.

Clinical Trial: a type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease.

DNA: the molecules inside cells that carry genetic information and pass it from one generation to the next. Also called deoxyribonucleic acid.

Difference between genomic and genetic testing: genetic testing detects hereditary alterations in DNA while genomic testing detects acquired alterations in DNA.

Gene: the functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein.

Genetic testing: the process of analyzing cells or tissue to look for changes in genes, chromosomes, or proteins that may be a sign of a hereditary disease or condition, such as cancer.

Genetic marker: a gene or short sequence of DNA used to identify a chromosome, or locate other genes on a genetic map.

Genetic profile: information about specific genes, including variations and gene expression, in an individual or in a certain type of tissue. A genetic profile may be used to help diagnose a disease or learn how the disease may progress or respond to treatment with drugs or radiation.

Genome: the complete set of DNA or genetic material present in a cell or organism.

Genomics: the study of the complete set of DNA (including all of its genes) in a person or other organism.

Genomic profiling: a laboratory method used to find out why some people get certain diseases while others do not, or why people react in different ways to the same drug.

Germline mutation: A gene change in a body's reproductive cell (sperm or egg) that becomes incorporated into the DNA of every cell in the body of the offspring. Germline mutations are passed on from parents to offspring.

Immune system: a complex network of cells, tissues, organs, and the substances they make that helps the body fight infections and other diseases.

Immunotherapy: a type of therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases.

Liquid biopsy: a test done on a sample of blood to look for cancer cells from a tumor that are circulating in the blood or for pieces of DNA from tumor cells that are in the blood. It may be used to help plan treatment, find how well treatment is working or if cancer has come back.

Molecular profile: technologies used to identify cancer biomarkers associated with either the response or the resistance to certain treatments. The information gathered is used to identify and create targeted therapies to work better for a specific cancer or tumor profile

Mutation: any change in the DNA sequence of a cell. Mutations may be caused by mistakes during cell division, or they may be caused by exposure to DNA-damaging agents in the environment. Mutations can be harmful, beneficial, or have no effect. If they occur in cells that make eggs or sperm, they can be inherited. Certain mutation may lead to cancer or other diseases.

Precision (personalized) medicine: uses information about a person and their cancer to select the best course of action for their specific situation.

RNA: one of two types of nucleic acid made by cells. RNA contains information that has been copied from DNA. Also called ribonucleic acid.

Targeted therapy: a type of treatment that uses drugs or other substances to identify and attack specific types of cancer cells with less harm to normal cells. Some targeted therapies block the action of certain enzymes, proteins, or other molecules involved in the growth and spread of cancer cells. Other types of targeted therapies help the immune system kill cancer cells or deliver toxic substances directly to cancer cells and kill them. Targeted therapy may have fewer side effects than other types of cancer treatment.

Other Biomarker Names:

MUTATIONS NGS
Biomarkers
GENES Genomics
Genomic testing
Tumor Markers
BIOLOGICAL MARKER DNA
Next Generation Sequencing
RNA Comprehensive Biomarker Testing
Broad Molecular Profiling

What Treatment Option is the Best for You?

You and your medical team are partners in making the decision on which treatment approach you will take to treat your cancer after all your questions have been answered. No matter what testing you have done, the results are combined with the best medical advice available to determine your options or know which medicines may not work for you. It may turn out that what is chosen is considered standard treatment.

STANDARD TREATMENT

Accepted as the correct treatment option for certain type of disease and is widely used by healthcare professionals.

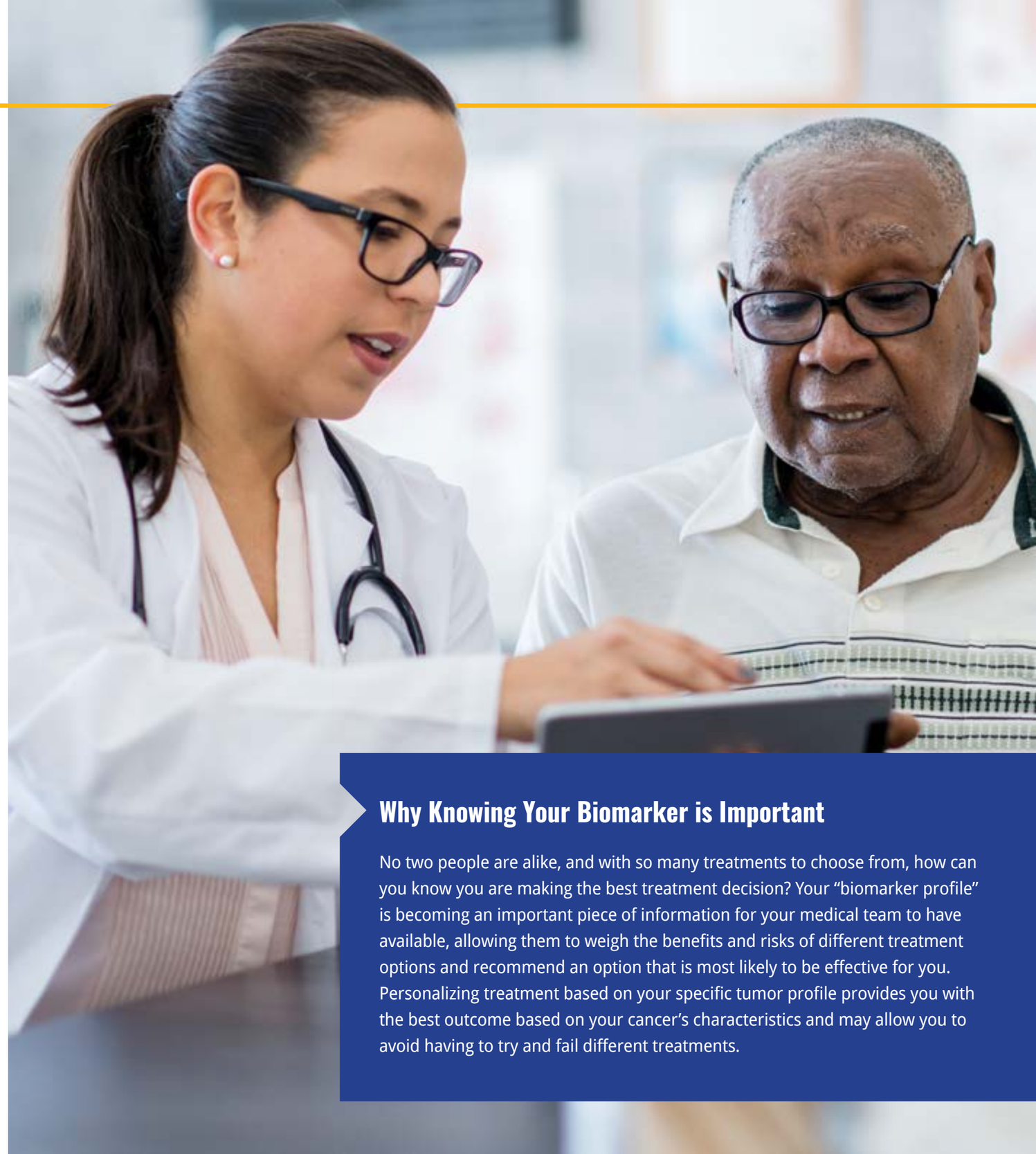
COMBINATION THERAPIES

Some cancers have treatment guidelines which can be a combination of therapies including chemotherapy, radiation therapy, immunotherapy, targeted therapy, and surgery.

LIMITED OPTIONS

Other cancers may have more limited options, often based on the stage and type of cancer. Identifying the characteristics in your specific cancer can be important in selecting the best treatment approach, which may include a clinical trial.

Before beginning treatment, you may want to seek a second opinion, when a doctor other than your current doctor reviews your medical records and gives an opinion about your diagnosis or how it should be treated. This second doctor's opinion may be the same as your current doctor or it may suggest a different approach for your treatment. A second opinion can help you feel more comfortable that you are choosing the right treatment plan and if the oncologists agree, you can feel extra confident.



Why Knowing Your Biomarker is Important

No two people are alike, and with so many treatments to choose from, how can you know you are making the best treatment decision? Your "biomarker profile" is becoming an important piece of information for your medical team to have available, allowing them to weigh the benefits and risks of different treatment options and recommend an option that is most likely to be effective for you. Personalizing treatment based on your specific tumor profile provides you with the best outcome based on your cancer's characteristics and may allow you to avoid having to try and fail different treatments.

Mutations and Access to Therapy

Currently, every identified mutation does not have an approved therapy.

Your oncologist will coordinate with a pathologist to make sure that your tissue or blood sample is getting the proper testing.

The pathologist ensures the sample is sent to the appropriate internal or external testing lab, in order to identify any genomic mutation(s) present in the sample.

It takes time for specific testing to be completed, so there may be a two- to three-week delay in getting test results back.

If you are newly diagnosed, the results of your genomic testing ensure all treatment options may be considered. Progress is being made towards developing therapies that target specific mutations known to play a role in cancer growth. One reason that this approach is becoming more popular is the hope that such targeted therapies might be more effective and/or less toxic than conventional therapy. It is important to note that these targeted treatments may not be covered by insurance without knowing biomarker testing results.

Once testing is complete, there is a chance your molecular profile suggests a treatment that is not an FDA approved indication for your diagnosis. This is known as being an "off-label" indication. Using a drug off-label for cancer treatment is not unusual, and insurance companies may pay for an off-label use as long as 1) the drug is listed on the drug formulary for your insurance plan and 2) the off-label use is listed in an approved drug compendium. If this situation applies to you, it can affect reimbursement by your insurance company. If you are denied coverage of a medication due to being an off-label indication, ask your doctor to provide documents to the insurance company supporting the use of the medication. **Patient Advocate Foundation** is here to help with appealing the denial obtaining the off-label medication.

Have More Questions About Biomarkers?

We're here to help.

patientadvocate.org

(800) 532-5274

Case Study

Clark Kent is a 66-year-old man with a four-month history of coughing up blood and pain in his chest with the cough. When he presented to the doctor, he was sent for a chest x-ray that showed a 6 cm mass, followed by a sputum sample which revealed abnormal cells suggestive of cancer. He had additional tests that included both CT and MRI scans, and followed by a biopsy performed via a bronchoscopy. Once the test results were analyzed it was determined he had non-resectable stage 4 non-small cell lung cancer. He was noted to have a mutation in the epidermal growth factor receptor (EGFR) gene of his cancer cells. As a result, instead of IV chemotherapy, he was recommended to begin treatment with an oral drug that targets the EGFR protein.

LUNG CANCER BIOMARKERS

- ALK
- BRAF
- EGFR
- MET
- NTRK
- PD-L1
- RET
- ROS1

What if My Doctor Does Not Bring Up Having Biomarker Testing Done?

1. **You need to have open channels of communication with your medical team to ensure you are getting the care you need and that you want.**

2. **Write down your list of questions about biomarker testing or additional treatment options before your next appointment.**

3. **Be sure that you list your most important questions first to make sure they get answered during your visit.**

Questions to Discuss with Your Medical Team

Get the most out of your care by becoming an educated health consumer. Ask questions, most people don't have personal experience discussing or dealing with biomarker testing.

TYPES OF TESTS AVAILABLE

What is the stage of my cancer and am I a good candidate for molecular genomic profiling?

Are there biomarkers applicable to my cancer that could provide insight on chemotherapy, targeted therapy, or immunotherapy?

Does my specific cancer have a molecular test available?

Will I need another biopsy to have the testing completed? Can testing be done using a blood test (e.g. liquid biopsy)?

FINANCIAL OPTIONS AND BILLING

How much will testing cost and will my insurance cover any of the cost?

What are my options if I cannot pay the out-of-pocket costs associated with testing?

Will I be billed separately for testing?

EXPECTATIONS BEFORE AND AFTER TESTING

Are there any risks to having more testing?

Will the test results influence my treatment options?

Who will perform my testing?

How reliable are the test results?

When is the best time for me to get biomarker testing done?

How long will it take to get the results back?

Will I be able to get a copy of my test results?

Will molecular profiling results include any clinical trials I may be eligible to join?

Genetic Counseling - Are you at Risk?

Prior to genetic testing, it may be helpful to work with your oncologist to setup an appointment with a genetic counselor to discuss personal and family medical history as it relates to your potential cancer risk.

GENETICS OR GENOMICS - WHAT IS THE DIFFERENCE?

While the terms sound similar, genetics and genomics have different roles to play in the health and disease arenas. Although both are involved in the study genes, that is where they differ.

Genetics

Refers to the study of genes and the role they play in which traits are passed down from one generation to another.

Genetic testing looks for inherited mutations that may increase your risk of developing cancer. *Hereditary or germline* testing is done to see if there are changes present in the DNA of the body's cells that occurred when a person was conceived. These changes can be passed from one or both parents and can pass from generation to generation. Having a germline mutation may put you at a higher risk of being diagnosed with a specific type of cancer, such as breast or colon cancer.

Genomics

Studies a person's genes with a focus on how the genes interact with each other within the person's environment.

Acquired or somatic mutations are the most common cause of cancer. The damage to the gene can occur at any time as the result of environmental factors (such as smoking, tobacco use and ultraviolet radiation). These mutations are present in the cancer tumor itself and are not passed from parent to child. Acquired alterations can have an impact on how a tumor responds to treatment.

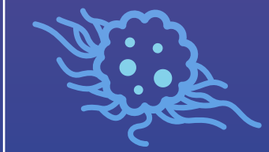
What is Biomarker Testing?

Biomarker testing identifies which genes, proteins, or molecules are present in a sample of cancer tissue, blood or body fluid and look for changes in the number or structure of those genes, proteins, or molecules. Whether and when biomarker testing should be done varies by cancer type and situation. Your medical team looks at your diagnosis and how the results may influence treatment choices before ordering biomarker testing.

The human body is made up of trillions of cells and it is estimated that one million cells die every second.

There are different molecules in the body, and each cell contains DNA and RNA (genetic codes you are born with) that serve as the cell's "brain" telling it how to behave, when to divide, and if damaged, when to die.

This is a good thing because it allows your body to take away parts of cells that were broken or not right from the start and replaced with new ones.



Unfortunately, cancer cells ignore signals to stop dividing or to die, but instead continue growing out of control, forming a tumor that may spread to other areas of the body.

Specific Tests May Inform Cancer Risk and/or Treatment

CHROMOSOME TESTING

Chromosomes are important because they are the structure where genes, which are segments of DNA, control how your body works by making proteins. Genes carry instructions that tell cells to make different types of protein that allows a cell to function properly. Each protein has a specialized function in the body. When there is a change or break in the process, it can create an abnormal protein. Abnormal proteins can cause cells to grow out of control and become cancerous. Cytogenetic tests are used to measure changes in blood, bone marrow, or other body tissues looking for chromosome abnormalities, referred to as biomarkers. Biomarkers can then be used to screen for or diagnose cancer. Most cancer cells contain more than one kind of chromosomal abnormality.

One of the best-known examples of this is the translocation of 2 chromosomes in chronic myelogenous leukemia (CML). This new abnormal chromosome is referred to as the Philadelphia chromosome and is found in almost all patients with CML.

MOLECULAR TESTING

Molecular testing, as the name implies, looks for changes in genes, proteins, or other molecules in a sample of tissue. This could be having more than one copy of a gene (duplication or amplified genes), missing parts of a gene (deletions), or can occur when a broken piece of a gene attaches itself to a totally different chromosome (translocated genes). In addition, gene testing looks for changes (mutations) in our genes and can identify the specific biomarker involved in the cancer. While this testing has traditionally been performed on small tissue samples, advances in liquid biopsies may be able to replace some tissue testing.

An example of molecular testing is in lung adenocarcinoma, when there is a mutation in the tumor EGFR (epidermal growth factor receptor) gene that produces an abnormal protein that can lead to the growth and spread of lung cancer.

BIOCHEMICAL TESTING

When a gene becomes abnormal due to a mutation, the proteins produced by that gene are also abnormal, allowing it to be measured as a biomarker. Abnormal proteins contribute to cancer growth. A biochemical test can be used to examine the abnormal protein but requires a tissue sample to complete the testing. Immunohistochemistry (IHC) is a form of biochemical testing that combines immunology and biochemical techniques to measure for both the presence and the amount of protein available in a tissue sample. This test also can be used to help determine whether a cancer is responding to treatment.

An area where this testing is involved is in breast cancer with HER2, estrogen receptor (ER) and progesterone receptor (PR) proteins. Being able to accurately determine the presence or absence of these proteins is important when determining appropriate treatment recommendations for breast cancer patients.

GERMLINE TESTING

Based on your family history your doctor may recommend you have germline testing. Germline testing checks a person's DNA for genetic mutations present from birth, that may increase your risk of developing cancer. Germline mutations are associated with a higher than normal risk for certain cancers including breast, ovarian, pancreatic, prostate, colorectal, and endometrial. By knowing if you have an inherited mutation you and your medical team can develop a plan to guide next steps for screening and whenever possible prevent cancer.

Lynch syndrome, the most common cause of inherited colorectal cancer, is also associated with a higher risk of developing endometrial cancer, among others. Germline testing can be done to see if there is a mismatch repair (MMR) protein or a deletion on the EPCAM gene to confirm the diagnosis. People with Lynch syndrome are more likely to be diagnosed at a younger age and are at an increased risk of developing multiple cancers in their lifetime.

Case Study

Jane Doe is a 55-year-old woman who felt a lump in her breast who underwent testing that included a diagnostic mammogram, ultrasound, a core needle biopsy, Chest and Abdominal CT scans, followed by a mastectomy. She was diagnosed with metastatic (stage 4) breast cancer. On analysis the tumor was found to be HER2 positive, but was Estrogen (ER) and Progesterone (PR) negative. Based on these results her oncologist recommended her treatment include a drug to combat the increased hormones along with a HER2 inhibitor.

BREAST CANCER BIOMARKER MUTATIONS

- HER2, ER, PR
- PIK3CA
- TP53
- BRCA1/BRCA2
- PD-L1

TYPES OF BIOMARKER TESTING

Other Tumor Marker Testing

There are other tumor markers that can be used as screening tools to find cancer early when it is most treatable, to help determine if your cancer treatment is working, help plan future treatment options, or show if your cancer has returned. These substances are often found in the body so a normal level may not always be zero.

An example of this type of testing would be prostate specific antigen (PSA), which is used as a tool to screen, diagnose, and monitor treatment response for prostate cancer patients.

As an informed patient you want to have a discussion with your medical team to see if there is a specific test they may recommend you have done and how the results will be used in making treatment decisions. You should contact your insurance plan prior to testing to see if the specific test being considered is covered and if so, what your cost share will be. **Patient Advocate Foundation** can support you with any insurance denial.

The presence of a tumor marker alone does not necessarily mean cancer is present or if the cancer has reoccurred. That is why this is one piece of information used in combination with other diagnostic tests.

Insurance Coverage of Molecular Genomic Markers & Testing

There is no guarantee that every biomarker test will be covered for every diagnosis or stage of cancer. If the decision is made to undergo biomarker testing there are some things to consider.

Commercial insurance generally covers testing based on your plan.

- Must be an FDA-approved test to be covered
- Coverage depends on your cancer diagnosis and stage
- Requires guidelines or evidence to support molecular testing for the specific tumor type and stage
- The results of testing should impact clinical decisions for care other than standard therapy
- Out-of-pocket costs you are responsible for include co-pay, coinsurance, and deductible, which vary by plan and where you are with meeting your out-of-pocket maximum

Medicare covers testing if the following conditions are met.

- For cancer patients with recurrent, relapsed, refractory, metastatic, and/or stages 3 or 4 of cancer
- If it is the first time having next generation sequencing testing for current cancer diagnosis or if a new primary cancer diagnosis has been made by the treating physician
- If the patient has decided to seek further cancer treatment (e.g., therapeutic chemotherapy)
- For patients with germline (inherited) ovarian or breast cancer

Whenever possible, it is best to contact the insurance company PRIOR to testing to ask about coverage requirements before the test is done

Questions to Ask Your Insurance Company Regarding Biomarker Testing

Do you need pre-approval from the insurance company for biomarker testing to be covered?

Is the specific biomarker test you are trying to obtain a covered benefit under your plan?

Is there a medical policy for biomarker testing or your specific test? If so, do you meet the criteria for "medical necessity" under the policy?

Is the test considered to be a companion diagnostic test? This is when a test helps match a patient to a specific drug or therapy. If so, it may be covered.

If not, your diagnosis or test may be considered "experimental or investigational" and not covered under your policy.

Do you have to use a specific testing facility for biomarker testing to be paid at an "in-network" rate?

Are you required to provide biomarker test results to your insurance company before they will approve a targeted therapy associated with a specific tumor marker for your cancer?

Do evidence-based guidelines, such as National Comprehensive Cancer Network (NCCN) or American Society of Clinical Oncology (ASCO) recommend biomarker testing as the standard of care for your diagnosis? Are these recommendations included in the approved guidelines?

What can you expect your out-of-pocket amount to be, including unmet deductible, copay, and coinsurance?

What if Your Claim or Request for Biomarker Testing is Denied?

Have you received a prior authorization denial, denial letter, or explanation of benefits (EOB) indicating no insurance payment for the test?

1. Call your insurance company and ask for additional details on why your claim or request was denied.
2. Partner with your oncologist's office when appealing a denial.
3. Deadlines are important, make sure your appeal is submitted on time.
4. Include any supportive evidence including approved guidelines as part of your appeal packet.

Appealing a Denial of Coverage

There is a chance your biomarker testing or treatments suggested from the results could be denied by your insurance company. If this is the case, you have the right to file a formal appeal to your insurance company asking them to reconsider their decision. For additional information on the appeals process, please refer to Patient Advocate Foundation's publication, *Tips for Appealing Health Insurance Denials*.

Scan Code to Download *Tips for Appealing Health Insurance Denials*

Financial Resources for Biomarker Testing

Your medical team is focused on making sure you have the best treatment and may not be aware of your financial concerns. It is important to communicate any concerns around cost with your treating provider to learn of any options you may have. **Patient Advocate Foundation** also remains committed to help you find solutions.

- **If you are uninsured or if your insurance does not cover biomarker testing,** call or check the website of the testing company to learn if they offer any financial assistance programs. If the testing will be completed in a medical center laboratory, a good contact is the financial counselor at the facility to see what, if any, assistance is available.

- **If you are insured,** PAF's Co Pay Relief Cancer Genetic and Genomic Testing provides a grant for qualified individuals when funds are available https://copays.org/

Biomarker Resources

https://www.mycancergenome.org/content/page/overview-of-targeted-therapies-for-cancer/

https://www.cancer.gov/about-cancer/diagnosis-staging/diagnosis/tumor-markers-fact-sheet

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Have More Questions About Biomarkers?

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