

## LEARN from the EXPERTS



## Comprehensive Biomarker Testing and Lung Cancer Overview

[Lorren] Thank you so much for joining us for the Caring Ambassadors Program video series, Learn from the Experts. Our main goal is to empower and educate patients and communities to be advocates for their health and to improve their lives.

Today's video is dedicated to living with lung cancer and it highlights one chapter from our book, Lung Cancer Choices. The video series is broken down into short segments, so it's easy to watch and navigate. You can watch the videos in any order, so feel free to choose what interests you the most.

I'm Lorren Sandt, the Executive Director at Caring Ambassadors Program, We're very excited to welcome nurse practitioner, Elizabeth Krueger. Liz will be discussing the chapter, Comprehensive Biomarker Testing, written by her colleague, Kelly Goodwin.

Elizabeth Krueger is a family nurse practitioner who specializes in the care of thoracic oncology patients at Massachusetts General Hospital. She completed her Bachelor of Science degree in Healthcare Policy and Management at Providence College and then went on to receive a Bachelor of Science in Nursing and Master of Science in Nursing from Regis College.

More than a dozen new drugs for the treatment of NCSLC have been approved since 2013, marking an exciting and hopeful time in lung cancer research and care. With improved biomarker testing techniques, an expanding list of molecular

targets, and more approved and emerging therapies, comprehensive biomarker testing is an essential part of the evaluation and management of all patients diagnosed with NSCLC. In this video, Liz will give an overview of comprehensive biomarker testing.

We hope that this video will provide helpful insights and information for patients and caregivers affected by lung cancer. If you're interested in learning more about the Caring Ambassadors Program and our mission to help patients with lung cancer, please watch the video series.

And please share this information with anyone who might find it useful. Together, we can make a difference in the lives of those affected by lung cancer.

Welcome Liz.

[Liz]Hello everyone, my name is Elizabeth Krueger, and I am a nurse practitioner at Mass General Hospital Cancer Center, and I work in the Center for Thoracic Cancers. Today we'll be talking about comprehensive biomarker testing in lung cancer.

Lung cancer is the most frequently diagnosed cancer in the United States and there are several different subtypes. Rates of the of lung cancer vary by sex, age, race, ethnicity, socio economic status, geography and lung cancer is found across all smoking histories. It's broadly classified as non-s small cell lung cancer and small cell lung cancer. Non- small cell lung cancer takes up the biggest piece of the pie and represents approximately 85% of total lung cancer diagnoses.

Adenocarcinoma, a subset of non-s small cell lung cancer accounts for 40%.

Squamous cell another subset of non-small cell lung cancer, accounts for about 30%, these two are their most common histologies of non-small cell lung cancer.

When we think about gene testing, we historically have focused on adenocarcinoma because those diseases have invariably had the most gene changes that have been found. But there are targets that are able to be targeted in squamous histologies.

When we think about lung cancer treatment we have historically thought about chemotherapy and used it in many different stages of disease. Chemotherapy indiscriminately goes after and kills cells that divide rapidly. There are unintended effects on normal cells that divide rapidly too. Hair cells divide rapidly and so

there's often hair loss associated with chemotherapy. The cells within the GI tract also divide rapidly and those are affected by chemotherapy causing nausea diarrhea and other associated side effects. Radiation therapy is also used alone or in conjunction with chemo or other modalities. Another pillar of lung cancer treatment is immunotherapy, and immunotherapy is used in both a curative and metastatic setting, and it works by looking at proteins on the cell surface and using those bonds to cause cell death. Surgical approaches are incorporated for both curative and curative intent therapies, and when we think about targeted therapies, the focus of our discussion today, we are looking at genetic alterations that are found in tumor tissue or blood. Patients are matched to available therapies based on gene changes that may be found. The majority of targeted therapy is reserved for the metastatic setting. But with certain subtypes it can be used as part of a curative strategy when coupled with other therapies like surgery in early-stage disease.

What are biomarkers? In order to understand biomarkers, we'll briefly overview genes in DNA. Humans have over 20,000 genes located on 46 chromosomes or 23 pairs. These genes are known collectively as the human genome. Genes are portions of DNA that contain instructions for making the molecules that help our cells to form and function. Errors in these codes result in gene changes. Through sequencing the genetic material of normal tissues cancer scientists have been able to identify genetic alterations often caused called mutations that interfere with the normal functioning of cells. Biomarkers are molecules in the blood or tissue that can result from mutations in genes. Biomarkers help to link subsets of patients to certain therapies. When your care team orders biomarker testing it's done to rule in or rule out the role of targeted therapy. Targeted therapy is typically a pill-based therapy that's taken on a daily or twice a day basis depending on the drug and depending on the target. Targeted therapy takes advantage of advantage of these gene changes by blocking proteins that signal cell growth and division.

There are different types of molecular alterations or gene changes. On the first figure on the left-hand side you'll see an example of a copy number alteration. The first picture shows a normal copy number of red genes on that genetic material. The second picture below demonstrates an example of amplification or extra gene copies of the red and blue genes as pictured in the image beneath. Rearrangements or fusions are another type of genetic alteration. Those are

abnormal juxtapositions of two genes which leads to a chronic activation and signaling of the cancer cell. Rearrangements and fusions effectively create a new gene stuck that in the on position, so it quickly replicates and causes the tumor cells to turn over. Some other cancer promoting mutations inactivate genes whose normal function is to stop or slow cell growth. There are other types of mutations called point mutations, deletions, insertions, or substitutions, or inversions. When we look at the example on the right-hand side you'll see the notation of wild type Beast. Wild type is the nomenclature that scientists used to denote normal genetic material or something that's expected, nothing abnormal. When we look at the letters in BEAST, BEAST codes for a protein made up of genes and at a certain address on the genome. So, BEAST stands for different proteins. So, if we were to substitute B for F you would be left with FEAST and so and so on with the other examples below. So, with any change in gene and change in protein, we have an error in the genetic makeup of that cell, which then can go on to replicate.

When we think about genetic alterations there are two buckets of alterations, there are germline alterations, and somatic alterations. Germline alterations are inherited DNA changes that are passed down from family member to family member through egg and sperm. These germline alterations can increase chances of developing a cancer in certain populations and may be associated with family history of cancers or a predisposition to an illness. These germline mutations are ideally identified in blood but also can be found in saliva or buccal mucosa with a Q-tip swabbing of the inner cheek. Occasionally, germline alterations can be incidentally detected during tumor testing. So, when we think about tumor testing it's different than germline testing or germline changes. Somatic alterations or changes in the tumor tissue are acquired after conception, or acquired after birth, and they are not inheritable, they are sporadic, and they can be affected by one's environmental exposures, your lifestyle choices, like smoking, poor diet, or through random errors during the process of cell growth and division that turn DNA into RNA.

Somatic alterations can be identified in the tissues as I mentioned but they can also be identified in the blood in certain situations, and you may have heard of a liquid biopsy or circulating tumor DNA that's when cancer cells are within the bloodstream and are captured on a blood draw. Somatic alterations can be targeted by cancer therapies.

When we think about biomarker testing there are two different main types of biomarker testing. One is tissue-based testing which is considered the gold standard. This tissue-based testing directly tests the tumor material for gene changes from a biopsy. The other option is called a liquid biopsy that looks for ctDNA or circulating tumor DNA. When we talk about liquid biopsies that's also a discussion about circulating tumor DNA or ctDNA that's when the tumor mass sheds cancerous cells into the bloodstream, and they are circulated. Blood is drawn, the specimen is spun down, and then the plasma is sent for analysis looking for genetic changes in that biopsy specimen. Liquid biopsies are less invasive, they're quick, they're easy to repeat at certain times during progression of illness, but the only caveat to that is that there needs to be circulating tumor cells in the bloodstream and order for it to be an appropriate test, and one that yields results. It's most often seen in metabolically active cancers. The sensitivity of detecting Target mutations with ctDNA is between 60 and 80% and again depends on tumor location, size, blood supply, and detection methods. These biomarkers help your care team to find out if there is a mutation in the tumor, and if so, a targeted therapy could be used. As we look and find these gene changes, it can open doors to new treatments. It can open doors to treatments that are FDA approved and on NCCN guidelines, but also to clinical trials that are looking to investigate some of these biomarkers further. Biomarker testing should be offered to all individuals with advanced squamous and non-squamous cancers, and increasingly the testing is being done on early-stage disease too, as it has implications for treatment prior to surgery and treatment following surgery. When your care team discusses biomarker testing you can expect to discuss a consent form and sign a consent form. A consent form is a permission slip that says that you've been fully informed, and you allow the test to be done. Part of the consent form typically discusses risks associated with tumor testing or biopsy and also with blood draws. Regarding tumor testing these tests are often done on archival tissue or tissue that had been sampled at the time of your diagnosis. Occasionally these tissue-based samples are repeated at the time of progression but that's on a case-by-case basis. Additionally, your care team will discuss any financial implications of these tests. So, these tests are typically covered by insurance but they're often some costs that can be incurred. And lastly there are risks of finding germline mutations, or mutations that are inheritable. The intention of the test is not to find a germline mutation but, occasionally we do find them, and if that does happen then it's a discussion with you and your

provider, and then you're typically referred to a genetic counselor to talk more about what that means for you and your family.

There are different methods to do biomarker testing. Hospital-based accredited labs can do biomarker testing in-house, other times we use commercial labs and send out either the ctDNA, or the tumor tissue. PCR or polymerase chain reaction as a single gene test that's used to look at a region of the chromosome it comes back quickly it comes back in about a week but there is a high false negative result, and it can exhaust a lot of the tumor tissue supply.

FISH or fluorescence in-situ testing looks specifically for rearrangements translocations and amplifications and a pre-specified mutation. This requires 50 to 100 well-preserved tumor cells in order to perform this test.

IHC or immunohistochemistry looks for proteins and cells or tissues that are overexpressed. This happens really quickly, and this is how we confirm PDL-1 testing which is necessary when we think about using immunotherapy.

Lastly, Next Generation Sequencing is, in my opinion, the gold standard. It's the most expansive. It can cover about 10 to 100 alterations, and it uses DNA. Fragments from the biopsy sample are isolated and then compared to a known mutation library and a normal reference sample. There are several hospital-based and commercial-based tests specifically tailored for lung cancer screening and testing.

When we think about non-small cell lung cancer, I've listed here some of the main biomarkers and mutations that we find on our gene testing in ctDNA. In 2021, the NCCN recommended biomarker testing for all advanced non-small cell and non-small cell cancers including squamous and non-squamous.

As we look at the chart on the left, EGFR mutation is one of the most common genetic mutations in lung cancer. It represents about 20% of non-small cell lung cancers and is seen in young persons with lung cancer with no, or light, smoking history. This is identified on PCR, or next generation sequencing. There are different EGFR mutations Exon 19 deletions and L858R are the most common. Exon 20 is a bit different and represents only about 2% of lung cancers. ALK

Anaplastic lymphoma kinase represents about 3 to 5% of lung cancers and is common in male non-smokers. This is detected by IHC and FISH.

ROS1 is another driver mutation and found in one to 2% of lung cancers, often found in younger, Asian, never smokers.

MET exon skipping or MET over expression is found in 2 to 4% of non-small cell lung cancers, often in older females, nonsmokers. MET over expression can sometimes be found as a resistance mutation, or when a person's been on a targeted therapy for a long period of time they can develop MET over expression and then a new drug can be tailored and added to your regimen.

And then as there are several other less common that I've listed here, but the one that I'd like to highlight is KRAS G12C. KRAS G12C is found in squamous and non-squamous lung cancers and is present in about 25% of lung cancers, that's a really high percentage and typically in smokers. There are some targeted therapies that can be used for KRAS G12C but those were approved in the second line, so after chemotherapy.

And then we look at then PDL-1 is also a key biomarker. PDL-1 expression on tumor cells is different. Different than the ones that we've been talking about today. It's a protein on the cell surface that indicates the role for immunotherapy and helps with decision-making about treatments for advanced lung cancers. An important take-home point is that immunotherapy is rarely or never combined with a targeted therapy in lung cancer because of the risk of significant toxicity.

[music]