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Molecular Testing in Advanced Non-Small Cell Lung Cancer

Announcer:
You're listening to *On the Frontlines of Non-Small Cell Lung Cancer* on ReachMD. Here's your host, Dr. Alexandria May.

Dr. May:
This is *On the Frontlines of Non-Small Cell Lung Cancer* on ReachMD, and I'm Dr. Alexandria May. Joining me today to discuss molecular testing in advanced non-small cell lung cancer is Dr. Timothy Burns. He's a Professor of Internal Medicine in the Division of Medical Oncology at the Ohio State University Comprehensive Cancer Center. Dr. Burns, welcome to the program.

Dr. Burns:
Dr. May, thanks so much for having me today.

Dr. May:
Well, let's start with the big picture, Dr. Burns. When a patient is newly diagnosed with advanced non-small cell lung cancer, what's at stake in the first treatment decision, and why do you want the molecular profile in hand before committing to a first-line regimen?

Dr. Burns:
That's a great question, and it's a really important question, because how our patients in the metastatic setting are going to do is going to be greatly dependent upon if they have one of these oncogenic drivers that we can target with a targeted therapy. And about half of our patients today with adenocarcinoma of the lung—which is the most common type of non-small cell lung cancer we see—and even some squamous cell carcinomas, will have a targetable alteration.

To put it in perspective, your average survival of a patient with metastatic non-small cell lung cancer today is still around 12 to 14 months. We have molecular drivers, where the progression-free survival—not the overall survival—is bordering eight years. So finding one of these alterations can turn a disease with a relatively limited survival into a disease that sometimes we think of as a chronic disease. So it's critical that we know we have the right target for these patients.

In addition, many of these patients that have a targetable alteration will not respond to immunotherapy. In fact, one of our best markers of who will respond to immunotherapy is having the proper testing done and showing that they don't have one of these drivers.

Dr. May:
In addition to the advanced setting, is molecular testing needed for early-stage or locally advanced disease?

Dr. Burns:
It is required, essentially, for anyone who has a tumor greater than three centimeters—so any stage II and up. And that's because, even in patients that don't have one of these drivers, one of the requirements to give immunotherapy up front in what we call the neoadjuvant setting depends on not having an EGFR or ALK alteration. And today, we already have three targeted therapies approved in the adjuvant setting, after surgery. That's for EGFR, ALK, and RET. And so really, any patient with any tumor greater than three centimeters should be getting molecular testing, and it will determine their care and outcomes.

Dr. May:
With that context in mind, what does comprehensive biomarker testing look like in your practice today? Specifically, which genes or alterations are on the panel?

Dr. Burns:

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It's gotten more and more complex, and I oftentimes talk about what we need for testing in 2026. And actually, it now does not only include a comprehensive DNA or next-generation sequencing, but also often RNA-seq and even immunohistochemistry, which we thought, with these newer assays, we'd get away from.

But there are now 20 markers that we look for today, and you really need a combination of next-generation sequencing—which is DNA-based—RNA sequencing, which can be very helpful, and FISH in some cases. And there are actually some markers that you can only find with immunohistochemistry. So we thought we'd be able to get rid of some of these older assays, but we really can't find these markers. And these include EGFR, BRAF, MET, HER2, KRAS, ALK, ROS1, and RET. There's NTRK1 through 3. There's MET amplification. There's high MET expression, high HER2 expression, PD-L1, and now, some emerging biomarkers such as MTAP, where there are a lot of trials ongoing. So it's gotten more and more difficult or challenging to get all the testing that we need, but it's never been more important.

Dr. May:
That's a great transition to my next question. What's your perspective on the limits of DNA-based panels for detecting fusions and MET exon 14 skipping? When do you add that RNA-based sequencing, and how do you make sure those alterations aren't missed?

Dr. Burns:
The DNA-based testing, again, for translocations or things like MET exon 14 skipping mutations—where it's a very small deletion or even amplification—can often be missed. However, if you do find a targetable oncogenic driver on your DNA-based testing, you can stop.

One of the things about these being these oncogenic drivers is they're mutually exclusive. So if you find a KRAS G12C, you're not going to find a ALK fusion or MET exon 14 skipping. But if you don't—some people have panels where they do this upfront—but if you don't find something on your initial panel, you need to keep looking.

And so that's often when we'll add RNA-based sequencing, which is better for fusions and MET exon 14 skipping mutations. But even with those two, you're going to be missing some. You obviously can't look for PD-L1, MET, or HER2 high expression. And you still will miss some amplification. It can become challenging when you don't find something. And I think, if you don't find anything on NGS and RNA-Seq, it's oftentimes we'll think about liquid biopsy. But if you find something, you can stop. If you don't, you, at a minimum, should be doing DNA and RNA-based sequencing.

Dr. May:
For those just joining us, this is *On the Frontlines of Non-Small Cell Lung Cancer* on ReachMD. I'm Dr. Alexandria May, and I'm speaking with Dr. Timothy Burns about best practices for molecular testing.

So how do you decide between tissue and liquid biopsy, and are there situations where you would use both?

Dr. Burns:
So the advantage of liquid biopsies is they're quick. Oftentimes, we're waiting for a result and, at our own institution, we're fortunate in that once it's sent, we're going to get a result back in 10 to 14 days. We don't have to send out to an external vendor, which can add time. But even in those cases, or if we have a small biopsy, where we don't think we're going to get all the testing done, many of the vendors for RNA-seq will get your result back in a week.

Now, the issue with liquid biopsy-based tests is they are rule-in, not rule-out tests. So, if you see a result, you can believe it. But if it's negative, it can be negative because the tumor may not be shedding enough DNA. So you can't stop with that. And that's one of the issues that we see, is that some people in the community will get a test and assume that a negative means the person doesn't have it. It's really that, if they have something, you can believe it. If it's negative, you have to keep looking for tumor tissue. And sometimes, you need to redo a biopsy. But if you find something on a liquid biopsy, you can believe it.

Dr. May:
We know that results can take a week or two to come back, and patients often feel symptomatic and anxious during the wait. So how do you navigate that window? Are there situations where you'd start treatment before the results came in?

Dr. Burns:
This goes into the whole patient journey, because, by the time they're seeing a medical oncologist, they may have had pneumonia for six months that their primary care kept giving them antibiotics for. They may have taken a while to get in with a pulmonologist, get the scans done, and get the biopsy, and maybe the first biopsy didn't work. And so there's all these things that have delayed their treatment, and some people can be quite symptomatic.

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I think it's important that, if someone is symptomatic, you treat them. And you can always give a patient a platinum doublet. Our normal standard of care for non-oncogene driver patients is a platinum doublet plus immunotherapy, or, if a patient has a high PD-L1, immunotherapy alone. But if someone's symptomatic and has a high disease burden, you normally have chemo involved. So you can always give a cycle of chemotherapy. That's going to buy you three weeks for your tests to come back.

The reason that we don't want to just jump in with immunotherapy is that many of the targeted therapies, if you give them after immunotherapy, will have severe side effects, and you're almost burning that bridge. And so, you do not burn any bridge. Even some clinical trials at this point have actually allowed a cycle of standard of care for some clinical trials by giving a cycle of chemotherapy.

So again, sometimes it's just reassurance, but if someone is symptomatic, it's very reasonable to just go ahead with a platinum doublet, and then ,by that time, you should have your plan in place.

Dr. May:
Now, zooming out again, what would you say are the most common reasons testing falls short in practice?

Dr. Burns:
It still is a lack of tissue, far and away. If you're in a large academic center where you have a very strong thoracic surgery, interventional radiology, interventional pulmonology—especially the pulmonology point, where they're going to be doing, six or seven passes. Often, I talk with my pulmonologist, and in the community, sometimes they'll do up to three to establish a diagnosis, meaning, yes, I have lung cancer. But really, for molecular testing, you need a lot more.

So it's really tissue that has always been the issue. And you can kind of get around that if you're fortunate with your liquid biopsy, but it's often just getting the right biopsy and then biopsying people again if you have to, or biopsying people at the time of progression, if, for some reason, they just didn't have proper testing up front.

Dr. May:
So what systems or techniques are most effective at addressing these challenges?

Dr. Burns:
If you're an academic medical oncologist and you're treating everything, it's really hard to keep up on what the 20-plus markers are now that we look at in lung cancer. It's setting it to some place that’s going to give you a comprehensive profile that then gives you some direction. So you don't have to check 20 different boxes to make sure that you get everything you want. And so that also means having, even in the community, a multi-disciplinary plan. Or maybe you're a thoracic surgeon or a pulmonologist, so you know you're getting the tissue you need, and then you have a pipeline.

And even silly—not silly stuff, but who sends it out, right? So the pulmonologist sees the patient, and depending on where you are, some pulmonologists will send it out. And that's fantastic, because then the patient shows up to your clinic, and either the result's back or it's been cooking, so to speak, for at least a week. So it's really establishing—whether it's formalized in your institution or in your practice—"If you do this biopsy for me, the expectation is that you're going to send this, and here's why." So I think that's what seems to be the most successful.

Dr. May:
I have one more question for you before we wrap up, Dr. Burns. If our audience were to change one thing about how they approach testing in newly diagnosed advanced non-small cell lung cancer, what should it be?

Dr. Burns:
I think it's making sure that you're sending a comprehensive panel. There are a lot of online resources now, but also just reach out if you're not sure about an alteration. But I think the single most important thing is doing a comprehensive panel, because, again, about 50 percent of our patients are going to have something targetable today.

Dr. May:
That's a great recommendation. A big thanks to my guest, Dr. Timothy Burns, for sharing his expertise on molecular testing in advanced non-small cell lung cancer. Dr. Burns, we appreciate you being here today.

Dr. Burns:
Thanks again for having me.

Announcer:
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