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Exploring Biomarker Testing in NSCLC: Current Guidelines & Testing Considerations

Announcer:
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This medical industry feature, titled "Exploring Biomarker Testing in NSCLC: Current Guidelines & Testing Considerations," is sponsored by Amgen.

Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
Lung cancer accounts for more deaths than colon, breast, and prostate cancers combined, with 2.2 million new cases and 1.8 million deaths worldwide every year.[1] In the United States, most patients with lung cancer (78%) are diagnosed with advanced or metastatic disease.[2] Overall, 85% of lung cancer cases are non-small cell lung cancer, or NSCLC.[3] But, survival outcomes for patients with non-small cell lung cancer have improved over the years,[4] due in part to smoking cessation and personalized medicine with novel therapies.[5,6]

This is ReachMD, and I'm your host Dr. Jennifer Caudle, and joining me to explore the role of biomarker testing in treating patients with non-small cell lung cancer is Dr. Ticiana Leal, a medical oncologist and Director of the Thoracic Medical Oncology Program in the Department of Hematology and Medical Oncology at the Winship Cancer Institute of Emory University School of Medicine. Dr. Leal has been compensated by Amgen for participating in this program.

Dr. Leal, thank you so much for being here today.

Dr. Leal:
Thank you. Thank you, Dr. Caudle. Thank you ReachMD. I'm very happy to be here today to have this discussion about biomarker testing.

Dr. Caudle:
As we know, there have been an increasing number of actionable biomarkers identified and targeted therapies approved for patients with NSCLC.[7] Can you explain how the biomarker landscape has evolved in recent years?

Dr. Leal:
Yes. Yeah, the number of actionable biomarkers in non-small cell lung cancer has certainly increased over time and in recent years.[7] In 2003, the *EGFR* gene mutation was identified as a molecular biomarker in non-small cell lung cancer.[8] And then subsequently, we learned about *ALK* rearrangements in 2011.[9] And since then, in the last decade, we've had several more molecular as well as immune biomarkers emerge to help clinicians personalize the treatment plan for their patients with non-small cell lung cancer.[7] The molecular biomarkers of relevance include *EGFR*, *EGFR* exon 20, *ALK* rearrangements, *ROS1* and *RET* fusions, *BRAF* V600E, *NTRK*, *MET* exon 14, and *KRAS* G12C. These may inform the selection of targeted therapy.[10,11] We also have immune biomarkers, such as PD-L1, which may help identify the appropriate immunotherapy.[12]

Dr. Caudle:
And, how common are molecular biomarkers in patients with non-squamous non-small cell lung cancer?

Dr. Leal:
Yeah, that's a great question. It certainly varies—some of them are quite rare. But a 2020 analysis of nearly 15,000 patients with non-squamous non-small cell lung cancer from the AACR GENIE database showed that about 40% of patients have an actionable molecular biomarker, with *EGFR* and the *KRAS* G12C mutations being the most common.[13] For example, when you think about the most common ones, *EGFR*, *KRAS*, about 1 in 3 patients have *EGFR* or *KRAS* G12C mutation.[13] In 1 in 8, or about 13% of patients, have the *KRAS* G12C mutation.[13]

Dr. Caudle:
Let's take a moment to review the current clinical practice guidelines for non-small cell lung cancer. You know, what do they recommend when considering biomarker testing in patients with advanced non-small cell lung cancer?

Dr. Leal:
The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, or the NCCN Guidelines® for non-small cell lung cancer, recommend broad molecular testing for eligible patients with advanced non-small cell lung cancer.[12] Guideline-recommended biomarker testing results may help improve outcomes in patients with advanced non-small cell lung cancer.[14] And to highlight this, there was a retrospective study using the Flatiron Health database that showed that adherence to testing for guideline-recommended biomarkers, such as *EGFR*, *ALK*, *BRAF*, *KRAS*, *ROS1*, or PD-L1, reduced the risk of mortality by 11%, regardless of the therapy.[14,*] And in this study, about 2 in 3 patients received the recommended test for any biomarker.[14,*] And this really demonstrates that there is room for improvement in biomarker testing rates.

[*]From a retrospective study of 28,784 patients diagnosed with advanced NSCLC from the Flatiron Health database between January 2011 and July 2019. Adherence to biomarker testing consisted of patients with evidence of testing for any biomarker, including *EGFR, ALK, BRAF, KRAS, ROS1,* or PD-L1 between 14 days prior to and 90 days after diagnosis of advanced NSCLC and the main outcome, overall survival, was agnostic to treatment. Multivariable analysis was adjusted for age at diagnosis of advanced NSCLC, sex, smoking status, and stage at initial diagnosis of NSCLC.

Dr. Caudle:
And what testing methods are used to identify molecular biomarkers?

Dr. Leal:
There are different ways that we can test for these molecular biomarkers. Molecular alterations can be detected by single-gene tests, multiplex, or broad testing, like next-generation sequencing.[15] And, while upfront broad biomarker testing may prove more cost effective and provide timely results, there are certain situations where single-gene and multiplex testing may still have an important role in, uh, doing this kind of testing.[16] Uh, the guidelines recommend broad biomarker testing. And this is important because it really allows for simultaneous detection of both actionable and emerging biomarkers, and important genetic alterations that impact care in a more timely way.[12]

Dr. Caudle:
And Dr. Leal, can you tell us when broad molecular testing can be considered? You know, what are some of the benefits?

Dr. Leal:
Yeah, broad molecular testing in patients with advanced non-small cell lung cancer with non-squamous histology really should be done at initial diagnosis.[15] First of all, it informs treatment planning, because it identifies actionable biomarkers for which we have targeted therapies.[15] In addition, by doing broad molecular-based testing, you can conserve tissue by testing for multiple biomarkers and using less tissue than a series of single-gene tests.[15] In addition, it can reduce costs and turnaround times, uh, if you compare it to single gene, sort of, sequential testing.[17] And, you can get all the results in one single report, instead of sort of having piecemeal reports come in, which make this, uh, very challenging, uh, to make treatment decisions in clinical practice.[15]

Dr. Caudle:
And now, clinicians can acquire samples for biomarker testing through tissue and liquid biopsy.[16] When should liquid biopsy be considered?

Dr. Leal:
Yeah, liquid biopsy has certainly increased in – in its use.[16] Tissue biopsy really has been sort of the gold standard in non-small cell lung cancer, but the liquid biopsy can address certain challenges.[16] It's minimally invasive, all it requires is a blood draw.[16] And it

allows for detection of biomarkers when tissue is not available,[16] or tissue fails, um sort of Q and A, or quality assessment for analysis. And it certainly does result in faster turnaround time than a tissue-based approach.[16] In 2021, the International Association for the Study of Lung Cancer (IASLC), created a Consensus Statement on Liquid Biopsy for Advanced Non-Small Cell Lung Cancer and they outline three different diagnostic strategies.[16] One is a sequential approach. The sequential approach is when tissue is available, you perform sequential sampling, so tissue followed by liquid to be considered.[16] The second approach would be a complementary one. When tumor tissue is limited for genotyping, you can do a complementary sampling. That means you do them at the same time. You do a concurrent approach of tissue and liquid biopsy.[16] And I would argue that this approach is probably increasing in a lot of practices around the country. The third approach is liquid biopsy first. When a tissue sample is unavailable for tumor genotyping, then liquid biopsy first approach is the way to go.[16] However, it's important to note that if the liquid biopsy results don't show an actionable mutation, then certainly we need to double check that result with a tissue test, when feasible, because the presence of a driver mutation can't be ruled out from a liquid biopsy sample alone in these cases.[18]

Dr. Caudle:
It's interesting. Now, Dr. Leal, now that we understand the benefits of broad biomarker testing in patients with advanced non-small cell lung cancer, can you tell us, you know, what are the current biomarker testing rates in this patient population?

Dr. Leal:
Yeah, so despite guideline recommendations for broad molecular testing in eligible patients with advanced non-small cell lung cancers,[12] certainly, uh, we have room for improvement for testing rates, particularly in the community setting.[19] We have real-world data from 2021 using a retrospective observational study by the Molecularly Informed Lung Cancer Treatment in a Community Cancer Network.[19] And we have 3,500 patients that were evaluated in, uh, the community practices with advanced non-small cell lung cancer in the US.[19] And it showed that less than 50% of the patients received testing for five key biomarkers in non-small cell lung cancer, including *EGFR*, *ALK*, *ROS1*, *BRAF*, and PD-L1.[19]

Dr. Caudle:
And how do these lower-than-expected biomarker testing rates impact racial and ethnic minority groups in the United States?

Dr. Leal:
There's certainly an even greater need to increase broad biomarker-based testing among racial and ethnic minority, uh, groups in the US.[20,21] Overall, there's low awareness and knowledge of genetic testing for cancer among African American, Hispanic, and Asian American minority groups.[21] In a retrospective study performed in 2021 of more than 10,000 patients with advanced non-squamous non-small cell lung cancer using, again, the Flatiron Health database, Black/African American patients had lower rates of testing with next-generation sequencing (43.8%) compared to 54.7% in White patients.[20,†,‡] And importantly, these patients had non-squamous histology, where testing rates have been historically higher.[20,†,‡]

†From a retrospective cohort study of patients with advanced/metastatic NSCLC (N=14,768) from ~800 sites of care identified via the Flatiron Electronic Health Record Database between 2017–2020. Of this study cohort, 10,333 patients had non-squamous advanced/metastatic NSCLC, from which 7,627 patients were White (n=6,705) or Black/African American (n=922).
‡White vs Black/African American patients Ever Tested ($P = 0.09$) and White vs Black/African American patients Ever NGS Tested ($P < 0.0001$).

Dr. Caudle:
And beyond race and ethnic disparities in biomarker testing, how does smoking history impact testing rates in patients with advanced non-small cell lung cancer?

Dr. Leal:
Biomarker testing gaps have been demonstrated in patients based on smoking history, and retrospective studies using *EGFR* testing data from nearly 12,000 United States veterans with advanced non-small cell lung cancer, published in 2021, showed that never-smokers have higher biomarker testing rates compared to current and former smokers.[22] Another retrospective analysis using the Flatiron Health database in 2021 of more than 7,000 patients with advanced non-small cell lung cancer, showed that nearly 11% of these patients had the *KRAS* G12C mutation.[23] And as we know, you know, *KRAS* G12C mutations can be seen in patients who have a history of smoking—and about 97% of patients have a history of smoking.[23] So, I think the lessons learned are that broad, uh, broad biomarker testing is recommended in all eligible patients with advanced non-small cell lung cancer, regardless of characteristics such as

smoking status, race, or age.[15]

Dr. Caudle:
And so, with that in mind, then what are some key practical challenges or barriers associated with biomarker testing?

Dr. Leal:
In 2018, IASLC created a global survey on molecular testing in lung cancer. About 300 healthcare providers from the United States and Canada reported multiple barriers that impact biomarker testing rates in non-small cell lung cancer.[24,25] And here are some of the barriers that we saw in this study. One are the cost and financial challenges, insufficient quantity of tumor cells or inadequate tissue quality, lack of sensitivity of the assay or failure of the assay with inadequate technical expertise in the laboratory, lack of awareness of the rapidly evolving guidelines by clinicians, and varying and extended turnaround time from ordering to receiving the molecular testing results.[24]

Dr. Caudle:
And given these challenges, what can clinicians do to really help improve biomarker testing rates?

Dr. Leal:
The key thing about doing molecular testing is that this is, uh, really an approach that requires the entire team.[18] So, from sample collection to standardized testing, establishing multidisciplinary teams, there's a lot of methods that clinicians can consider to overcome these barriers for testing, and implementation in clinical practice.[18] So, one of the things we heard about is inadequate quantity and quality of tissue is commonly reported as a key barrier.[24] So, adopting a standardized method for specimen evaluation may be beneficial.[18] And one of the techniques that has been, uh, sort of reported as an important one to potentially overcome this barrier is a method called ROSE, or rapid on-site specimen evaluation, where pathologists and trained healthcare providers can look at the sample and confirm that it's adequate for testing.[26] This may reduce biopsy, uh, re-biopsy rates as well.[26] Another thing that we've talked about, and there are some challenges with that, but could really help is the implementation of "reflex ordered testing", which means that as soon as there is a diagnosis of non-small cell lung cancer, that there is an automatic reflex ordering testing procedure to really, uh, trigger doing molecular testing at that clinical practice.[27] This is important because you can really reduce the time from diagnosis to initiation of the appropriate therapy for the patients as well.[27]

Dr. Caudle:
So, Dr. Leal, you mentioned that a multidisciplinary team, or MDT, can help clinicians tackle practical challenges they may face. Who are the key members of an MDT and what makes them successful?

Dr. Leal:
I'm a big fan of MDT. I mean, the multidisciplinary team, uh, includes a very broad range of different healthcare providers and team members that really move the field forward and provide excellent clinical care.[28] And it may include radiation and medical oncologists, thoracic surgeons, pathologists, pharmacists,[29] pulmonologists, radiologists, or advanced practice providers and nurses as well.[28] And of course, you know, with the patient at the center. The patients are key members of that multidisciplinary team.[28] And that's why we have it. "Multi-D" teams are often a way to, uh, work together to develop standardized practices for reporting and documenting molecular test results efficiently and appropriately.[18] And communication is key to maximize the role of the team and improving patient care.[28] So, here are some thoughts and considerations. With a "Multi-D" team, you know, we can discuss testing for both actionable and em – emerging biomarker, uh, at diagnosis for all patients,[30] identify recent approvals,[31] and update the team about the guideline recommendations that are rapidly changing,[32] share best practices to optimize tissue collection and processing,[16] review when tissue and/or liquid biopsy testing may be appropriate,[16] and consider implementing standardized reporting and test results and documentation.[33]

Dr. Caudle:
That's so helpful. And I'm really glad that we're covering this concept of multidisciplinary teams. As a family doctor myself, uh, I certainly believe in the importance of them, so that's wonderful. And – and now before we close, Dr. Leal, do you have any final thoughts on biomarkers, testing patterns, and ways to help improve biomarker testing rates in patients with advanced non-small cell lung cancer?

Dr. Leal:
Right. So, I mean, to close out, I think it's really important to – to take home that guidelines for non-small cell lung cancer recommend that all eligible patients with advanced non-small cell lung cancer, regardless of smoking history, or race or age, should undergo broad biomarker-based testing.[34,35] And there are benefits for the broad, uh, based testing, which include the ability to test for all the

actionable and emerging biomarkers at the same time, potentially saving time and costs, as well as minimizing the amount of tissue required for biomarker testing, and the test results that will guide the use of targeted therapies or immunotherapies.[15] Despite guideline recommendations,[12] testing rates can be improved, particularly in the community setting.[19] And we definitely can do better. And finally, to help improve biomarker testing rates, clinicians should consider different methods to overcome these testing barriers that we talked about. Some of this can include the implementing of, you know, tissue assessment on site at the time of the biopsy,[26] reflex ordered testing,[27] standardizing the reporting of biomarker testing results, and certainly working together or establishing a collaborative "Multi-D" team.[18]

Dr. Caudle:
Excellent. Well, with those final considerations in mind, I'd like to thank my guest, Dr. Ticiana Leal, for sharing her insights on biomarker testing in non-small cell lung cancer. Dr. Leal, thank you so much for being here today.

Dr. Leal:
Thank you. Thank you, doctor.

Announcer:
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Acronyms
AACR=American Association for Cancer Research; ALK=anaplastic lymphoma kinase; BRAF=proto-oncogene B-Raf; EGFR=epidermal growth factor receptor; IASLC=International Association for the Study of Lung Cancer; KRAS=Kirsten rat sarcoma; MDT=multidisciplinary team; MET=mesenchymal-epithelial transition; NCCN=National Comprehensive Cancer Network; NGS=next-generation sequencing; NSCLC=non-small cell lung cancer; NTRK=neurotrophic tyrosine receptor kinase; PD-L1=programmed cell death ligand 1; RET=rearranged during transfection; ROS1=c-ros oncogene 1; ROSE=rapid on-site specimen evaluation.

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