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Spotlight on KRAS G12C: Biomarker Testing Considerations in the NSCLC Landscape

**Announcer:**
You're listening to ReachMD. This medical industry feature, titled "Spotlight on KRASG12C: Biomarker Testing Considerations in the Non-Small Cell Lung Cancer Landscape," is sponsored by Amgen.

Your host is Dr. Paul Doghramji.

**Dr. Doghramji:**
Non-small cell lung cancer is characterized by an expanding number of genomic alterations that drive the initiation and maintenance of the tumor growth.[1] And since many of these genomic alterations (such as *EGFR, ALK, ROS1*) have targeted therapies available and others (like *KRAS G12C and HER2*) that are under investigation,[2,3] testing for these biomarkers is crucial, as it tells us about a patient's unique lung cancer, which ultimately impacts the treatment plans.[1] That's why today, we're taking a closer look at the guideline recommendations for biomarker testing as well as best practices for overcoming real-world issues that are often encountered.

This is ReachMD, and I'm Dr. Paul Doghramji.

Joining me is Dr. Alex Spira, Medical Oncologist at Virginia Cancer Specialists and Dr. John Longshore, Director of Molecular Pathology at Carolinas Pathology. Dr. Spira and Dr. Longshore, welcome to you both.

**Dr. Spira:**
Thanks for having me.

**Dr. Longshore:**
Thank you.

**Dr. Doghramji:**
To start us off, Dr. Spira, can you tell us about the complex landscape of driver mutations in non-small cell lung cancer?

**Dr. Spira:**
So, in the era of precision medicine, we started to realize that cancer in general, and non-small cell lung cancer in particular, is a disease of the genome. Advances in genomic profiling have enabled the identification of driver mutations, which have led to a paradigm shift in treatment of patients with non-small cell lung cancer.[1,2]

About two-thirds of patients with lung adenocarcinoma in the United States have a driver mutation.[2] These driver mutations serve as biomarkers that provide insight into the patient's likelihood of responding to certain targeted therapies. A targeted therapy acts on specific genetic mutations.[2,4,5]

Some of the genetic alterations, like *EGFR, ALK, MET, RET, BRAF, ROS1, and NTRK*, have approved targeted therapies available. They are what we call actionable biomarkers, meaning that the presence of these alterations may predict response to treatments.[2,4,5]

Other genetic mutations, like *KRAS and HER2*, are considered emerging biomarkers[2,3] since therapies aimed at these are still under investigation and not yet approved.[2,3]

**Dr. Doghramji:**
And in terms of comparative prevalence rates, Dr. Spira, which driver mutations are more common than others?

**Dr. Spira:**
So, in the Western population, *KRAS* is the most prevalent driver mutation, with about a 25 percent prevalence rate,[2,6] followed by *EGFR*, which appears in about 15 percent of patients with lung adenocarcinoma.[2]

There are many known point mutations in *KRAS*, and among them, *KRAS G12C*, which stands for glycine-to-cysteine substitution at codon 12, is one of the most common.[7,8]

It accounts for about 13 percent, or roughly 1 in 8 patients, with non-small cell lung cancer[9] and about 3 percent of patients with colorectal cancer and about 1 percent of patients with pancreatic cancer.[10] Mutations of *KRAS G12C* result in dysregulation of the downstream signaling, uncontrolled cellular proliferation, and cancer growth.[11-13]

*KRAS G12C* mutation is truncal. These mutations arise early and persist as the disease devolves. Accordingly, if a patient tested positive, this will not change in case of progression.[14,15]

**Dr. Doghramji:**
Thanks for explaining that, Dr. Spira. And now turning to you, Dr. Longshore, can you give us a quick overview of the current guideline recommendations for biomarker testing?

**Dr. Longshore:**
I would be happy to. This is a landscape that is continually evolving and many new emerging and actionable biomarkers have been identified over the past few years.[1]

Clinical societies, such as the NCCN, CAP, IASLC, and AMP, have published guidelines that help provide guidance on how to test for these biomarkers. Some guidelines recommend testing for actionable and emerging biomarkers at the diagnosis of advanced non-small cell lung cancer[16-19] and also in some cases, at disease progression. Many professional guidelines recommend testing for emerging biomarkers as part of an expanded panel or in some cases single-gene testing.[16-19] According to these guidelines, clinicopathologic features such as age or smoking status should not be used to select patients for biomarker testing to improve the detection of clinically relevant genetic alterations.[1,17] As an example, *EGFR* mutations and *ALK* rearrangements, which frequently occur in never-smokers, have also been seen in patients that smoke.[20]

Even though KRAS mutations typically occur in current and former smokers, these mutations have also appeared in never-smokers.[21]

**Dr. Doghramji:**
And expanding further on that, Dr. Spira, how does *KRAS* factor into current guidelines?

**Dr. Spira:**
NCCN Guidelines are evidence-based and consensus-based guidelines. They recommend that testing for *KRAS* mutations may be useful because[17] the presence of a mutation in KRAS identifies patients who are unlikely to benefit in further molecular testing since driver mutations are typically mutually exclusive and non-overlapping.[17]

CAP, AMP, and IASLC Guidelines are evidence-based guidelines most recently published in 2018, and they recommend testing for *KRAS* as part of an expanded NGS panel or as a single-gene test to exclude patients from expanded panel testing.[16]

**Dr. Doghramji:**
So, now that we have a better understanding of the current guidelines, Dr. Longshore, what methodologies or testing modalities are available to detect *KRAS* mutations?

**Dr. Longshore:**
That's a great question. The *KRAS* mutations were described decades ago and were some of the original mutations that we saw in non-small cell lung cancer.[8]

*KRAS* can be tested using established molecular test methodologies, such as single-gene PCR or expanded next-generation sequencing panels.[16,18] A number of currently available next-generation sequencing platforms already report the *KRAS* status.[22-24] Regardless of which platform is utilized, it is important to consider reporting specific point mutations, as in the case of *KRAS*, the *KRAS G12C* mutation as an example.[25]

The turnaround time is typically shorter for single-gene tests compared to broad next-generation sequencing panels.[1]

The relative cost for a single gene test may be low.[26] However, studies have demonstrated that multigene panels may be more cost efficient in the long run than running multiple single gene tests,[26-28] and, in fact, our professional organizations all call for comprehensive genomic profiling for non-small lung cancer patients.[16,18]

**Dr. Doghramji:**
So, Dr. Longshore, are the recently approved actionable biomarkers like MET and RET, along with emerging biomarkers, tipping the scales towards increase in use of multigene panels?

**Dr. Longshore:**
It certainly seems so. We have now seven actionable biomarkers in non-small cell lung cancer, [1,29-31] and there are also emerging biomarkers that encourage us to use comprehensive genomic profiling or broad panel-based testing.[1,29-31]

That being said, each organization should do the analysis and consider tissue stewardship factors, streamlining the patient experience, and the overall cost to decide what platform they utilize. The overall goal, no matter the methodology, is to focus on providing the patient with the most appropriate therapy in a timely fashion.[19,32,33]

**Dr. Doghramji:**
For those just joining us, this is ReachMD. I'm Dr. Paul Doghramji and with me to discuss the importance of biomarker testing in non-small cell lung cancer are Drs. Spira and Dr. Longshore.

So, Dr. Longshore, earlier you have explained that current guidelines recommend biomarker testing for eligible patients with advanced non-small cell lung cancer, but is that actually seen in practice?

**Dr. Longshore:**
Unfortunately, it is not. There are studies that indicate that a significant number of patients with advanced non-small cell lung cancer do not receive adequate biomarker testing.[34,35]

In fact, one retrospective study conducted from 2017 to 2019 showed that only[35] 22 percent of patients treated at community oncology centers across the United States received testing for all guideline-recommended biomarkers, and at that time, that would be *EGFR, ALK, ROS1, and BRAF*.[35]

Data also suggest that a high proportion of patients, possibly up[35] to 50 percent who receive testing,[35] may not go on to receive an indicated targeted therapy.[35]

**Dr. Doghramji:**
In your opinion, Dr. Spira, what are some of the challenges that delay patients getting tested and ultimately receiving the most appropriate targeted therapy?

**Dr. Spira:**
One of the primary issues facing both oncologists and pathologists is staying up to date with the rapidly changing non-small cell cancer landscape and translating the evolving guideline recommendations into clinical practice.[34] For oncologists, this is important because they need to know which tests to order for their patients with non-small cell lung cancer.[32] Pathologists, on the other hand, need to have their labs set up in order to run these tests.[16,33] A second issue of concern is often complete biomarker status results take several weeks to come back,[34,36] and physicians may be inclined to initiate treatment without waiting for results.[19]

**Dr. Doghramji:**
And just as a quick follow-up to that, Dr. Spira, what are some potential solutions to overcome these obstacles?

**Dr. Spira:**
So, it's recommended by NCCN Guidelines for treating physicians to wait for molecular testing results for actionable biomarkers in eligible patients with advanced non-small cell lung cancer before beginning first-line therapy, if clinically feasible.[17]

In addition, experts have recommended implementing reflex testing protocols where physicians don't need to specify the biomarker tests for each patient, but pathologists initiate testing at time of diagnosis.[19]

This has been shown to increase the number of patients who receive testing for these guideline-recommended biomarkers as well as increase the number of genetic alterations detected.[19,37]

It's also been shown to significantly reduce time to treatment. Establishing a reflex testing program should, of course, be an institutional

decision. An strategy can be put into place with an open dialogue between pathologists and other members of the oncology team.[19]

**Dr. Doghramji:**
Dr. Longshore, from your vantage point, what are some of the challenges you encounter that contribute to this lack of biomarker testing?

**Dr. Longshore:**
In pathology, one of the most common issues encountered is the lack of adequate tissue quantity and quality for all needed biomarker testing.[1,32,34] In fact, some studies have shown that up to 25 percent of tissue samples have inadequate tumor for biomarker analysis,[32] which might then require a rebiopsy, which can be challenging from a risk, cost, and patient preference standpoint.[1,19] Also, biomarker tests, when performed as a series of single gene tests rather than as a broader, more comprehensive panel, tend to use more tissue, which can potentially limit the number of molecular tests that can be run in the future.[1]

**Dr. Doghramji:**
So, with those issues in mind, then, Dr. Longshore what's been recommended to helps address these obstacles?

**Dr. Longshore:**
The amount of tissue collected at biopsy should be maximized as best as possible.[1]

To help with this, rapid on-site evaluation, or ROSE, can be performed during the biopsy to assess both the quantity and quality of tissue and tumor collected.[38] If insufficient tumor is procured, the sample collection can be immediately repeated. ROSE has been shown to increase the number of samples that are adequate for molecular testing.[38]

The NCCN Guidelines recommend that pathologists utilize techniques to optimize tissue handling and maximize the amount of tissue available.[17]For example, laboratories can develop dedicated protocols for small biopsies, which can include upfront slide sectioning for both diagnostic and biomarker testing.[17,19] The NCCN Guidelines also recommended avoiding overuse of immunohistochemistry for the diagnosis of lung cancer and to help conserve tissue for downstream molecular testing.[17]

**Dr. Doghramji:**
And from your experience Dr. Spira, are there any other options available for clinicians who are faced with this challenge?

**Dr. Spira:**
Yes. Liquid biopsy also is a potential solution when tissue samples are limited or not available or if a patient is unfit for an invasive biopsy.[39]

Studies have shown that clinically relevant genetic alterations can be detected in these liquid biopsies as well as in tissue with a very high concordance rate.[40] The advantage of liquid biopsy is that it's less invasive than tissue biopsy, so highly acceptable by patients, with a turnaround time of less than seven days.[39-41] It can also capture tumor heterogeneity from primary tumor and metastases and can also be used to serially monitor response as well as detect acquired resistance as they emerge.[42] However, not all tumors shed DNA, so there's many false negatives.[39] In the case of negative findings, guidelines recommend analyzing a tissue sample.[16]

**Dr. Doghramji:**
And before we close, Dr. Longshore, any final thoughts on how to navigate this complex and rapidly evolving biomarker landscape in non-small cell lung cancer?

**Dr. Longshore:**
Yes. It is recommended to consider upfront molecular testing in a broad panel-based approach, most typically using the technique of next-generation sequencing at the time of diagnosis of advanced non-small cell lung cancer.[1]

Patients who have not received upfront molecular testing could potentially be delayed in receiving an appropriate therapy,[37] and there also may also be complications associated with testing at a later point in the disease course.[26]

It is important to ensure that testing results are clearly documented and are also readily available to the oncologist;[32] so if the patient relapses, these results could be utilized without the need for retesting.[32]

**Dr. Doghramji:**
Well, with these tactics in mind to address current challenges with biomarker testing for driver mutations including KRAS G12C and other driver mutations in non-small cell lung cancer, I would like to thank my guests Dr. Spira and Dr. Longshore for sharing their insights and recommendations on some of the testing and reporting barriers in both the clinic and the lab setting. It was great having you

both on the program!

**Dr. Longshore:**
Thank you very much.

**Dr. Spira:**
Thank you.

**Announcer:**
This program was sponsored by Amgen. If you missed any part of this discussion, visit Reachmd.com. This is ReachMD. Be part of the knowledge.

ALK, anaplastic lymphoma kinase; AMP, Association for Molecular Pathology; BRAF, proto-oncogene B-Raf; CAP, College of American Pathologists; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; IASLC, International Association for the Study of Lung Cancer; KRAS, Kirsten rat sarcoma; MET, mesenchymal-to-epithelial transition; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; NTRK, neurotrophic tyrosine receptor kinase; PCR, polymerase chain reaction; RET, rearranged during transfection; ROS1, c-ros oncogene 1.

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