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COMMENTARY

Biomarker Testing for Actionable Alterations in NSCLC—Perspectives from US-Based Academic and Community Oncologists: A Podcast

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ABSTRACT

The identification of actionable oncogenic driver mutations in patients with non-small cell lung cancer impacts therapy selection, and appropriate therapy administration results in improvements in clinical outcomes. Although biomarker testing for actionable oncogenic driver mutations is recommended in national and international guidelines, there are still unmet needs in the real world. Through this podcast we provide, from a US perspective, an overview and discuss challenges in biomarker testing from both an academic and a community oncologist viewpoint. We describe the importance of comprehensive testing, actionable biomarkers as recommended by guidelines such as National Comprehensive Cancer Network® (NCCN®) and European Society for Medical Oncology, types of tests and assessment techniques for detection of actionable biomarkers, and challenges in testing. These challenges include the lack of awareness of the biomarker testing guidelines among physicians, inconsistent reimbursement, longer turnaround time resulting in delays in therapy initiation, and nihilism associated with particular patient characteristics. To tackle these challenges, we offer recommendations from the perspective of our own clinical settings.

Keywords: Actionable biomarkers; Biomarkers; NSCLC; Sequencing

DIGITAL FEATURES

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PODCAST TRANSCRIPT

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Dr. Wade Iams: Well, welcome to the podcast, biomarker testing for actionable alterations in non-small cell lung cancer—perspectives from a US-based academic and community oncologist.

I'm Dr. Wade Iams in thoracic medical oncology at Vanderbilt University Medical Center, here with my colleague Dr. Konduri.

Dr. Kartik Konduri: Hi, I am Kartik Konduri, I am a part of Texas Oncology and I'm part of the broad network of US Oncology, but primarily work at Baylor University Medical Center, where we work at the Lung and Esophageal Cancers Research center in Dallas. So, I'll kick off. The first part of this discussion is about biomarker testing and why is it important in non-small cell lung cancer.

As we all know, non-small cell lung cancer is the most common type of lung cancer, and of course it comprises a multiple type and variety of histologies [1, 2]. We all know that some of the major types include adenocarcinomas and small squamous cell carcinomas, but of course there are certain other types including some smaller incidences of large cell carcinomas and large cell neuroendocrine carcinomas, etc. [2]. And, you know, over a period of time, we have seen that the prognosis for non-small cell lung cancer has been steadily improving because of our ability to understand the disease process better, understand molecular drivers, and utilize immunotherapies [3, 4]. So, in this section, we'll have a chat about the considerations for prognosis and how we are utilizing biomarker testing.

Dr. Wade Iams: Absolutely. Totally agree, Dr. Konduri, and one way that I explain the situation of biomarker testing in patients with non-small cell lung cancer when I'm having conversations with patients is the unfortunate reality that most patients have stage four disease at diagnosis. And the overall prognosis, historically, when we look at chemotherapy, and even immunotherapy, for the medians, the median survival is still within 1 to 2 years with treatment for those patients [5, 6]. So, it's a very severe prognosis. And I talk in terms of the three broad categories of treatments we have today and the ways to beat the average, the three broad, broad categories being: cytotoxic chemotherapy; immunotherapy, most commonly pembrolizumab with or without chemotherapy for these patients; and then oncogene-directed targeted therapies [3, 4].

And really to beat the average, if you're eligible for an oncogene-directed targeted therapy, you'll typically beat the average. And if you have exceptional benefit from immunotherapy, then you can really blow the average out of the water.

So that's kind of what we focus on, and really highlights the importance of biomarker testing in estimating the patients who may beat the average with immune therapy with very high PD-L1 scores, for example, and of course identifying patients eligible for oncogene-directed therapies.

Dr. Kartik Konduri: You bring up a very good point. As we have gone through the last many years, perhaps the last decade, we have been able to pick up more and more biomarkers that we are using.

And there are guidelines by various international guideline agencies that talk about doing testing in appropriate circumstances and how to test for not just predictive, but prognostic, biomarkers, and the consideration for evaluation of these biomarkers and how to use them for targeted therapies for our patients [7, 8]. That is something what we sort of say is personalized medicine. And there have been many treatment approvals in the last few years, including immunotherapy, as you talked about, Dr. Iams, and then considerations for targeted therapies.

And as we have gone through these discoveries and have started using these medicines in our clinic, the incorporation in terms of how to test for these in an effective manner, it becomes of paramount importance. And, because of that, it sort of behooves us to understand the perspectives of how to test and how to treat our patients in this situation.

So, from a community perspective, I would say that the importance of biomarker testing, of course in all non-small cell lung cancer, is very paramount, but in a community perspective there still remains a big gap in terms of testing as well as its utilization in the personalized therapy for our patients.

We will try to explore this over a period of time, but we've seen that many of our community practices still struggle with the ability to do testing. There are certainly improvements and trends over the last few years about testing in the various community practices that I interact with, but nevertheless, some more ground needs to be covered and it's still a work in progress.

What are your experiences, Dr. Iams?

Dr. Wade Iams: I think a lot of the push in academics is to getting the biomarker testing done as a reflex.

And in my mind, there's really two broad categories of biomarkers that we're testing for: generally PD-L1 by immuno-histochemistry, and our broad-based next-generation sequencing testing which is more involved and generally takes longer; it's not just an overnight immunohistochemistry stain [9–11].

And recently at Vanderbilt, we have been successful at getting reflex testing done so that for all non-small cell lung cancer diagnoses, PD-L1 and a broad-based next-generation sequencing panel is initiated by pathology. For the last several years, that process had to be initiated by medical oncology. And I think that's okay, but there's sometimes a few weeks' interval between that diagnosis and patients being able to establish in the oncology clinic, so really trying to narrow that turnaround time.

And one of the things that's actually helped reflex being approved across the medical center, and this is right here from academic colleagues as well, is the fact that it's not only just stage four patients now that can benefit from this biomarker testing.

With the introduction of immunotherapy and *EGFR* inhibitors, osimertinib, for patients with resected non-small cell lung cancer, now it's relevant for patients with early stage disease [7]. So that was really a decisive argument within our medical center that, hey, now all our patients need it, it's not just stage four patients.

So, it's given the pathologist more comfort in reflex ordering, and knowing that it's going to be clinically relevant. I don't know if that's also been a factor for you as well.

Dr. Kartik Konduri: I echo that completely. At Baylor University Medical Center, we have been doing reflex testing in all stages. And, as you rightly mentioned, it has become more relevant and pertinent to multiple stages across non-small cell lung cancer therapy.

And it is something that I hope my colleagues in community practice will also pick up and the trend will improve. Of course, there is still some way to go, as I mentioned just now, and the hope is that, as time goes by, in the near future, many more test evaluations will be through a reflexive way if possible.

And if not, at least in a time-efficient manner such that it's applicable for the treatment for our patients in a quick turnaround time.

Dr. Wade Iams: Absolutely.

We're going to talk a bit about the common biomarkers in non-small cell lung cancer, so just getting into the details a little bit, kind of distinguishing the three broad categories. The three broad categories of biomarkers that we think about in patients with non-small cell lung cancer are diagnostic, prognostic, and predictive.

Diagnostic biomarkers we're all very familiar with, such as TTF-1 Napsin A to diagnose an adenocarcinoma subtype, and P40 to diagnose a squamous subtype in a patient with non-small cell [7, 12]. Those are diagnostic biomarkers that pathologists are very facile with using to identify patients there.

Prognostic biomarkers are biomarkers that don't have therapeutic implications for what treatment will work but provide insight into likely outcome [7]. Specifically, TP53 in patients with non-small cell lung cancer has been associated across scenarios to have a worse prognosis [13].

Then, predictive biomarkers are those biomarkers that can tell us the likelihood of benefit from specific therapies [7, 14]. These include PD-L1, the higher PD-L1, of course, predictive of increased likelihood of benefit from pembrolizumab, the most common immunotherapy, or other PD-L1 inhibitors in patients with non-small cell lung cancer [15].

And then Dr. Konduri, I want you to talk a little bit more about those oncogene-directed targetable mutations. We've got so many now and it's a really different world these days.

Dr. Kartik Konduri: It certainly is. And, hopefully we just continue to find more and more of these markers that we can use to help our patients.

And of course, as you mentioned, there are so many, such that immunotherapy has its own. And now we are talking about targeted therapies with *ALK* arrangements with *BRAF* and *EGFR* mutations, *HER2* mutations, and *KRAS* mutations, of course, and *MET*ex14, and there are other *NRG1* fusions, *NTRK* fusions, etc., which are also rarer subtypes of markers, but are certainly prevalent in the non-small cell lung cancer space [7, 16].

But we have certain treatments which are very effective. For example, for *NTRK*. But I would also say that there are other new things that we are looking at, like *MET* amplifications and *HER2* amplifications, which can sometimes be associated with the resistance mechanisms, and in some circumstances, etc. [7, 16].

This is an exciting time for non-small cell lung cancer. And, as we go along, we hope to find more markers that we can have effective treatment strategies for our patients.

Dr. Wade Iams: Absolutely. It's an exciting time and we continue to identify new targets with new targeted therapies. I think it's very important to follow this research as it evolves within thoracic oncology.

Dr. Kartik Konduri: We want to talk a little bit about actionable biomarkers, and how do you test, and what are the guidelines and what treatment recommendations are considered for these guidelines in this section.

Between the various biomarkers that we have talked about, as, just in the prior section, what kind of evaluation should you undertake? And there are national guidelines, institutions including NCCN Guidelines®, ESMO and other practice guidelines, as well as pathology-based tissue testing guidelines that are also available for testing [7, 8, 17].

And how do you test them in a particular manner that is efficient, which conserves tissue, which has the ability to do the testing in an effective turnaround time, such that we can test for all these potential actionable mutations or gene alterations and be able to get a result in one shot rather than having to go reflexively multiple times, so that it does not waste time for putting in therapy for our patients.

And the NCCN Guidelines and the ESMO clinical practice guidelines are available for anyone to look at [7, 8]. And I would urge people to look at them so that they can get a broad understanding of how to recognize—or which biomarkers to recognize—that are currently in practice.

Dr. Iams, your thoughts?

Dr. Wade Iams: Yep, absolutely agree.

And the way that I think of the way the guidelines are written, it pretty much leads to where we have therapeutic applications for these oncogenic drivers.

Just quickly, because we've got so many, but it's amazing to just rattle through what are all recommended to be tested for in patients with non-small cell lung cancer.

We've got *EGFR*, *ALK*, *ROS -1*, *BRAF*, particularly V600E, where we can treat that, *NTRK* fusions, *RET*, *MET*, *HER2*, *KRAS*, particularly *KRAS* G12C, and PD-L1 [16].

It's a world that's rapidly expanded over the last several years, and I think it's important to make sure that, within our practices and institutions, all of the potential biomarkers are included in the panels that we're using, and that we're not just doing a focus panel for two or three of these, because we're now up to around ten or so biomarkers that should be tested in patients with non-small cell [7].

Dr. Kartik Konduri: Yes, it's important for our colleagues and everyone to understand that, in the non-small cell lung cancer world, we are testing everyone all the time reflexively, as you pointed out just a few minutes ago. And the testing is based on the fact that there's a non-small cell lung cancer. But then—and not necessarily just the histology or the clinical parameters of the patient—testing for these biomarkers helps to identify a potential treatment that can be a game changer in how patients are treated, and their prognosis and their outcomes [3, 16].

Dr. Wade Iams: Absolutely. Let's talk about this, I think this is a really fun section, talking about the ways to test for these biomarkers.

Specifically, kind of this ongoing debate within the field is about different ways to

practice between just using the tumor, sample or tissue-based testing, or liquid biopsy or blood tests.

Just curious, your practice is there any difference in what particular setting you may be in, and how you do that and how do you think about doing one or both?

Dr. Kartik Konduri: Yes, you are absolutely right. You know, I think because of certain limitations of tissue [3, 18–20], and we will talk about that, in terms of trying to get an adequate sample, or how the tissue is processed, and where it is being processed and held. Many of our clinical colleagues have also fallen on doing peripheral blood circulating tumor DNA profiles, and that's caught up a lot in the community practice as far as I can tell. There are of course some caveats, and people I'm sure understand that, and we'll discuss that for a second. One of the considerations for circulating tumor DNA is, of course, the good quick turnaround time and the ability to find the marker [20].

If you do find it, the specificity is high, and the test is probably truly correct in terms of being able to pick it up [3, 18]. The drawback is of course when there is a concern for tumor shedding, or there's not adequate amount of circulating tumor DNA in the blood, or if they are sensitivity rates are in the range of 60–70%, so there's a false negative rate that you can have, which then allows for a slip, as I might say, if one just relies on the peripheral blood [21, 22].

So, many of our colleagues in the community are looking at doing concordant testing sometimes because the tissue is not adequate and they don't want to just rely on this, but in some other circumstances it's to try to improve pick up rates [20]. And I must say that there's been a lot of acceptance of peripheral blood for circulating tumor DNA in the community.

Dr. Wade Iams: Absolutely. I think as you noted, the specificity of the liquid biopsy or circulating tumor DNA that, if that finding is present, it's accurate and actionable, plus the turnaround time, are the biggest appeals to me.

I think the reality is that I do still think that tissue biopsy is the gold standard, mainly just because of sensitivity, that it's higher than the liquid biopsy [3, 18, 19, 23].

But over time, and as we've seen in the use of these biomarkers within practice, that turnaround time can be a major factor. One anecdote that I think about, and what really this type of scenario that you see intermittently has pushed me to, is to send tumor and liquids simultaneously.

You know, patients with very aggressive disease who you'd want to know whether they're going to be eligible for an oncogenic driver seem to have a particularly poor prognosis [6]. Getting that information within a week can be a big deal. One patient of mine, newly diagnosed, had a moderate smoking history of probably anywhere from 20 to 30 packs a year, which impacts the likelihood of finding a targetable mutation. We sent both the tissue and liquid, but sometimes our tissue assay can take up to three to four weeks to get the result. And so they were progressed all the way to the ICU before we had the tissue results. And we got liquid results with a *KRAS* non-G12C mutation, a TP53 mutation. So, we have more closure that in that case it was actually not that they had an actionable mutation.

But there was, you know, tons of push from the family. "Couldn't we do a pill? Can we do a pill?" When we have that information quickly, we know that it's specific, and that these *KRAS* mutations, by and large, tend to be pretty exclusive of other oncogenic drivers and associated with the smoking history [8, 24].

Scenarios like that I think can be very helpful. We've gotten the information, and subsequently it was corroborated by the tissue in which we see good concordance between tissue and blood. But tissue can pick up mutations that blood doesn't. And the converse scenario that I think about is a patient with no smoking history. I'm much more cautious to draw conclusions from a liquid biopsy, particularly if that liquid biopsy doesn't have other mutations.

If it's just nothing detected, then you probably don't have much tumor shed. And so really waiting for the tissue in those scenarios, and maybe even repeating a biopsy if you don't have sufficient tissue for a patient with no smoking history, who you don't identify anything on

liquid biopsy, I think is an important component there.

And I think it can be helpful to also kind of talk about just the fundamental difference between our PD-L1 assessment which is an overnight immunohistochemistry stain logistically in the pathology lab done the same way as TTF-1 Napsin A.

Those diagnostic biomarkers and next-generation sequencing and kind of how next-generation sequencing has evolved from the initial tests for *EGFR* and *ALK*, which many times were single gene tests for a specific canonical *EGFR* mutation by PCR or just testing for an *ALK* rearrangement with FISH [9, 11].

And what the research has shown is that it's actually inefficient to try to do these tests piecemeal rather than to do a full, broad-based biomarker panel [25]. So, not sure. I'm curious. Within your practice and experience, do you still have much single gene PCR going on or much FISH going on?

Dr. Kartik Konduri: Yeah, so firstly, I absolutely agree with everything that you just said there. Non-small cell lung cancer is a difficult disease [6], you want to know its treatments quickly. There's a lot of awareness in the patient population about testing and how it can apply to their near and dear loved ones for treatment [26]. But coming to your point about evaluation with single gene panels, etc., in our center, we are doing reflexive next-generation sequencing, which is the broad-based testing. But you are right. Still, I do see many of my community oncology colleagues are still having reports in their hands, which are potentially single gene tests or sometimes multiplex PCRs, but many times these are not broad-based genetic evaluations. And, therefore, there is somewhat of a drawback in terms of how to so interpret these. And sometimes when these patients are referred to us for further evaluation, we somehow have to go back to the drawing board and start rechecking everything again just to make sure that we haven't missed something that might have not been done. So, there is potentially a gap that we would like to catch up with and cover in the community practices.

Some of that might be just related to where the tissue is procured and obtained, while some of that is related to the local standard in the hospital, in the community, in the community hospitals, and how the test has been done in the past and whether there is a change in the paradigm in terms of their testing.

Of course, as you say, tissue is still the more important thing [3].

We cannot make a diagnosis of lung cancer through peripheral blood and would certainly caution for that. And PD-L1, as you rightly pointed out, has to be still done by the tissue. But these are quick tests that we can turn around, and where it comes to evaluation for the broad-based genetic testing, the reflex testing considerations that we brought up a little while ago has been something that we have seen in our center to be very helpful. The pathologist is able to get a lead on doing the test, and by the time the patient is able to see us, we many times—if not all the time—are able to get some results. And it is very helpful to sort of see, especially amongst the most important markers, and sometimes some markers which are potentially investigative in nature, to decide for the future as to what one would want to do.

Dr. Wade Iams: I think that this has been a great discussion on those techniques, and, to perhaps sum up just a bit, I think for our guidelines we're noting that there are a couple of standard practices for doing this biomarker testing in patients with non-small cell lung cancer [7, 8, 17, 27]. One that some folks are choosing to stick with is tissue first, and if tissue's insufficient or if there are issues there, then to reflex to liquid biopsy assessment or the concomitant or simultaneous tissue and liquid tests [3, 28].

So, for me, I'm in that concomitant camp doing them both at once for the reasons we've discussed, and I think it's interesting to see how the field will evolve there.

Dr. Kartik Konduri: Absolutely agree. I think that, as techniques are improving, the turnaround times will improve, and the sensitivity rates will also improve for peripheral blood, so hopefully we will be able to do better and more for our patients.

Okay, so in this section, we are going to talk a little bit in detail about what our challenges on unmet needs are in biomarker testing in

non-small cell lung cancer. As we have mentioned just now, there's been a lot of concern that tissue is not easily available and there's a whole circumstance of trying to get it biopsied properly; get the tissue accessed properly; get it tested properly; and so that the test results come in time and in an interpretable fashion for our oncologist colleagues to get our treatment plans set up for our patients [28].

With that, I will ask my colleague Dr. Iams to give his inputs about what he thinks in terms of what the unmet needs are in the academic circumstances, but overall as well.

Dr. Wade Iams: I think turnaround time is still the biggest unmet need [29].

Sensitivity is a bit of an unmet need, and then making sure that we have the full breadth of testing is a major unmet need [29]. I'll just take those one by one. For the turnaround time, I think there are multiple factors in the process that lead to that, the reality that next-generation sequencing takes time to do; it's not just an overnight stain, this is DNA sequencing with technology that's evolved from our original Sanger sequencing approach, but still takes a matter of days at least and typically over a week [17, 28].

And you've got to get the tissue cut; you've got to get it sent to these labs that are doing the broad-based testing. Those labs have quality control processes that the tissue has to pass before the sequencing can actually be completed, and then of course you have the reporting step [28].

The multiple steps in the process all contribute to the turnaround time issues. I think making sure that the testing is done reflex, and refinement with technology over time, I'm hopeful that we'll continue to improve the turnaround time, which is one of the most important factors for our patients.

Sensitivity is another that's a particular area of research focus for me. It's the evolution of the sensitivity of liquid biopsy assays [3, 28]. There are fascinating new approaches. I won't get into too much detail but seeking to really increase the sensitivity of detection of tumor DNA, particularly for our MRD or minimal residual disease applications, can have big implications for the liquid biopsy sensitivity so that we don't miss things as much as we may miss today by just doing liquid biopsy [30].

And then, finally, I think that making sure that the broad-based testing is done is something that I see, and when I look at the data about getting all biomarkers tested, I think it's just a reality of process change over time, which has been at times imperfect as it always is. But initially we only had a few biomarkers that were relevant in patients with non-small cell lung cancer, so in-house labs created a single gene PCR or even a multiplex PCR as you've mentioned, and a FISH or a couple FISH for *ALK ROS-1*, etc. and they did their own thing for these limited biomarkers. But the pace of research has really been very fast, and we've rapidly gotten to ten or so biomarkers that need to be tested in patients with non-small cell lung cancer [7, 8], and some processes have just not kept up.

The data, noting the lower rates of testing when I look at the details, to me it just relates to that process which hasn't kept up with the research as it's exploded, and it [the research] has gone so fast [29].

But do you feel that similar things as far as just process improvement for a broad panel could really cover a lot of the issues we're seeing?

Dr. Kartik Konduri: I think that's a good point. I mean, its process improvements, and there are other small things that I think we need to talk about.

I mean, it's awareness of testing. As you rightly said, the pace of discovery and pace of data information about treatments and their efficacies, and how to incorporate these treatments has really just exploded in the last 5–10 years [5].

And then keeping pace and knowing all these, and follow-up is an important part of the consideration. If one looks at how the academics versus community oncology practices have looked from where I come from in US oncology, there was a trial called the My Lung Trial that was evaluated and which suggested that, in a huge proportion of patients when they at least tested for about five biomarkers over the last few years, less than 50% of the

people had all the tests and received their information prior to their first-line therapy [31].

Of course, over a period of time the mutational testing rates have increased. EGFR and PD-L1 particularly have taken off and improved, and there's been an increased up-tick in terms of recognition of these markers that have been present for a long time, and we have effective therapies that are touted and therefore many people have increased their testing [32].

There are reports that suggest that up to 80% of tests in community centers have shown *EGFR* testing, *ALK*, *ROS-1*, and *BRAF*; they sort of fall back a little bit, but they are still adequately tested [33]. But the incidences go down as the mutation rates or the mutation incidents gets rarer [29]. Very few of these rare mutations are tested and, unfortunately, that is a gap in our practice settings.

And it may be something to do with how the pathologists and the oncologists share their data, how the tissue is procured, and how the testing is done, as we just talked about.

Many of the national guideline institutions will say, do broad-based next-generation sequencing, but that's not necessarily happening everywhere [29]. Our intention and hope would be an improvement in terms of my colleagues where they are assessing and discussing with their pathologist. The utilization of these tests results may come slowly for patients because, as you pointed out, time is also of the essence, and some of my colleagues are hard pressed to potentially start treating these patients sooner than later. I would of course say that, in circumstances as such, we recognize this consideration where patients might have to go through treatment fast in a fashion to help control their symptoms, but potentially one can tailor these treatments such that we can do chemo, cytotoxic chemotherapy, quickly to try to help control some symptoms, but, at the same time, have our mind or an eye set out for these various mutations or markers that can help guide us.

Or, against certain therapies in the ensuing shortcoming future for these patients, my feeling is that there is a need for more awareness of how to do the testing in a broad-based next-generation sequencing fashion in various pathology departments, as well as in the oncology community.

And I hope that things like further education, involvement of molecular pathologists in interning, discussion with molecular tumor boards, and explaining the various mechanisms of how to do testing, the various paradigms of collecting tissue and testing it, educating our pulmonary and interventional radiology colleagues about getting adequate amount of tissue, is where I think things will help change the process in the community setting.

Dr. Wade Iams: Absolutely. And one thing I'm curious whether you run into it, I'll tell you in the landscape at our institution, which I think is reimbursement as we don't want patients getting big bills for these tests and we hope that our reimbursement processes keep up as well, so we typically bill insurance for these tests and many times it's covered. Sometimes insurance is not covering these tests. Fortunately, in those circumstances we work with Tempus and they have a very generous financial assistance program, so it's very rare for patients to owe anything, at most, a hundred dollars, for this next-generation sequencing testing.

Are you seeing issues with reimbursement and barriers there?

Dr. Kartik Konduri: It is certainly there, the reimbursement is definitely an important point that you bring up. While I was getting ready to talk about this podcast, I was reading some information where I was dismayed to see that there was a paper that suggested that only 10% of the actionable of the reporting costs were covered by payers, and there was a huge gap between denials and acceptable outcomes [34].

There are treatment options that are available for our patients and if payers don't cover these, it becomes a major issue. Then testing doesn't happen, and then we never get to find out whether there are these rarer actionable alterations, genomic alterations, that we can use to help our patients.

It definitely is an important thing. I'm hoping that, as the awareness of these tests continues to rise in the community and in the insurance industry, people will start understanding that it is an important part of our therapeutic, or actually, I should say, diagnostic

landscape without which we cannot move forward with treatment in non-small cell lung cancer in this day and age, and it's only going to get more complicated as we are going to have hopefully more markers that we can assess in the future.

Dr. Wade Iams: Absolutely. And I think a good point, and, getting close to the end, noting these advances in oncogene-directed targets, we've actually also expanded to patient populations who previously may not have had these options. And what I'm alluding to there is the fact that particularly patients with *KRAS*-G12C mutations can have really significant smoking history, so we certainly don't avoid biomarker testing in any of our non-small cell lung cancer patient populations [7, 8, 24].

And when you look at the data from big clinical trials for these oncogene-directed targeted therapies, it's usually single-digit percentages, 1–3% of patients with squamous histology can also have these mutations, particularly *MET* exon 14 skipping mutations [35]. So, we're also not only treating or only testing our adenocarcinoma patients but now we're testing all patients with non-small cell lung cancer.

It is rare in those with squamous histology, but possible. So, wondering what you're seeing as well regarding those additional factors, smoking history and squamous histology, is that impacting the testing that you're seeing?

Dr. Kartik Konduri: I think clinical parameters have had an impact in how our colleagues will ask or not ask for testing. And I think it's very important, as you pointed out, that people understand that all non-small cell lung cancer patients should be considered, not just on the pace of histology or issues in terms of what their clinical characteristics are, whether it's just a smoking history or not, and that these should not be taken into account in terms of testing [7, 29].

It is something that is known to occur, and, of course, as reflex testing takes into consideration that we just see a diagnosis of non-small cell lung cancer, hopefully that will override this consideration of limitation in terms of the clinical parameters, because we certainly do see squamous cell patients who sometimes have a marker and who could be treated with targeted therapy.

We see patients who have a long-term history of cigarette smoking and still have a marker, which, as you rightly pointed out in certain cases, are very much present, and sometimes there is still a rare marker, which can be evaluated for gratifying treatments for those patients. So, it should not be something that should be limited only to a certain population of clinical parameters. It does happen and it is to be hoped that, over a period of time, it continues to evolve such that everybody's tested with non-small cell lung cancer diagnosis.

Dr. Wade Iams: Absolutely. I think that's a good segue into our conclusions. And, in conclusion, thank you very much for your time and joining us for this discussion. I think that some key points that we've noted are the importance of broad-based testing for all patients with non-small cell lung cancer, regardless of stage, including all of our actionable biomarkers, which are ten plus at this point in patients with non-small cell lung cancer.

Understanding some of the process details, how NGS is really the way of the future, and efficient, and being keen on refining those processes within all of our institutions.

Dr. Konduri, other conclusions as well?

Dr. Kartik Konduri: From a community perspective, I would say that understanding how these tests are done and how to interpret them. The uniformity of tests is an important thing for our community oncology colleagues, and learning with the help of a molecular tumor board, with a molecular pathologist to help guide you and understand what might or might not be a variant of uncertain significance versus a real actionable driver, etc., would be a leap for the future where our patients will get a better treatment opportunity instead of just being evaluated on clinical parameters.

The take-home point, from a community perspective, would be to engage with our pulmonary and pathology colleagues to come up with a plan in your own institution such that you can have these tests with the broad-based next-generation sequencing testing, and perhaps involve the help of a molecular pathologist, as the landscape is becoming very

complicated, to understand what may or may not be a therapeutic treatment option.

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REFERENCES

1. Rodak O, Peris-Díaz MD, Olbromski M, Podhorska-Okołów M, Dzięgiel P. Current landscape of non-small cell lung cancer: epidemiology, histological classification, targeted therapies, and immunotherapy. Cancers (Basel). 2021;13. https://www.mdpi.com/2072-6694/13/18/4705.

2. Cancer of the Lung and Bronchus (Invasive). SEER Cancer Statistics Review 1975–2017. Available from: https://seer.cancer.gov/archive/csr/1975_2017/results_merged/sect_15_lung_bronchus.pdf. Cited 26 May 2023.

3. Pennell NA, Arcila ME, Gandara DR, West H. Biomarker testing for patients with advanced non-small cell lung cancer: real-world issues and tough choices. Am Soc Clin Oncol Educ Book. 2019;39:531–42. https://doi.org/10.1200/EDBK_237863.

4. Shields MD, Marin-Acevedo JA, Pellini B. Immunotherapy for advanced non-small cell lung cancer: a decade of progress. Am Soc Clin Oncol Educ Book. 2021;41:1–23. https://doi.org/10.1200/EDBK_321483.

5. Chen R, Manochakian R, James L, Azzouqa A-G, Shi H, Zhang Y, et al. Emerging therapeutic agents for advanced non-small cell lung cancer. J Hematol Oncol. 2020;13:58. https://doi.org/10.1186/s13045-020-00881-7.

6. Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk

factors, treatment, and survivorship. Mayo Clin Proc. 2008;83:584–94. https://doi.org/10.4065/83.5.584.

7. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.3. 2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed 23 Apr 2023. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

8. Hendriks LE, Kerr K, Menis J, Mok TS, Nestle U, Passaro A, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023;S0923–7534:04785–8. Available from: http://www.annalsofoncology.org/article/S0923753422047810/fulltext. Cited 7 Feb 2023.

9. Bruno R, Fontanini G. Next generation sequencing for gene fusion analysis in lung cancer: a literature review. Diagnostics. 2020;10:521. https://www.mdpi.com/2075-4418/10/8/521.

10. Jain D, Roy-Chowdhuri S. Molecular pathology of lung cancer cytology specimens: a concise review. Arch Pathol Lab Med. 2018;142:1127–33. https://doi.org/10.5858/arpa.2017-0444-RA.

11. Dong J, Li B, Lin D, Zhou Q, Huang D. Advances in targeted therapy and immunotherapy for non-small cell lung cancer based on accurate molecular typing. Front Pharmacol. 2019;10. https://doi.org/10.3389/fphar.2019.00230.

12. Tsuta K, Tanabe Y, Yoshida A, Takahashi F, Maeshima AM, Asamura H, et al. Utility of 10 immunohistochemical markers including novel markers (desmocollin-3, glypican 3, S100A2, S100A7, and Sox-2) for differential diagnosis of squamous cell carcinoma from adenocarcinoma of the lung. J Thorac Oncol. 2011;6:1190–9. https://doi.org/10.1097/JTO.0b013e318219ac78.

13. Gu J, Zhou Y, Huang L, Ou W, Wu J, Li S, et al. TP53 mutation is associated with a poor clinical outcome for non-small cell lung cancer: evidence from a meta-analysis. Mol Clin Oncol. 2016;5:705–13. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5228103/pdf/mco-05-06-0705.pdf

14. Ballman KV. Biomarker: predictive or prognostic? J Clin Oncol. 2015;33:3968–71. https://doi.org/10.1200/JCO.2015.63.3651.

15. Davis AA, Patel VG. The role of PD-L1 expression as a predictive biomarker: an analysis of all US Food and Drug Administration (FDA) approvals of immune checkpoint inhibitors. J Immunother Cancer. 2019;7:278. https://doi.org/10.1186/s40425-019-0768-9.

16. Kerr KM, Bibeau F, Thunnissen E, Botling J, Ryška A, Wolf J, et al. The evolving landscape of biomarker testing for non-small cell lung cancer in Europe. Lung Cancer. 2021;154:161–75. https://doi.org/10.1016/j.lungcan.2021.02.026.

17. Lindeman NI, Cagle PT, Aisner DL, Arcila ME, Beasley MB, Bernicker EH, et al. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors. J Thorac Oncol. 2018;13:323–58. https://doi.org/10.1016/j.jtho.2017.12.001.

18. Saarenheimo J, Eigeliene N, Andersen H, Tiirola M, Jekunen A. The value of liquid biopsies for guiding therapy decisions in non-small cell lung cancer. Front Oncol. 2019;9. https://doi.org/10.3389/fonc.2019.00129.

19. García-Foncillas J, Alba E, Aranda E, Díaz-Rubio E, López-López R, Tabernero J, et al. Incorporating BEAMing technology as a liquid biopsy into clinical practice for the management of colorectal cancer patients: an expert taskforce review. Ann Oncol. 2017;28:2943–9. https://www.sciencedirect.com/science/article/pii/S0923753419353815.

20. Sehayek O, Kian W, Onn A, Stoff R, Sorotsky HG, Zemel M, et al. Liquid first is "solid" in naïve non-small cell lung cancer patients: faster turnaround time with high concordance to solid next-generation sequencing. Front Oncol. 2022;12. https://doi.org/10.3389/fonc.2022.912801.

21. Cho M-S, Park CH, Lee S, Park HS. Clinicopathological parameters for circulating tumor DNA shedding in surgically resected non-small cell lung cancer with EGFR or KRAS mutation. PLoS ONE. 2020;15:e0230622. https://doi.org/10.1371/journal.pone.0230622.

22. Fernandes MGO, Cruz-Martins N, Machado JC, Costa JL, Hespanhol V. The value of cell-free circulating tumour DNA profiling in advanced non-small cell lung cancer (NSCLC) management. Cancer Cell Int. 2021;21:675. https://doi.org/10.1186/s12935-021-02382-0.

23. Aisner DL, Rumery MD, Merrick DT, Kondo KL, Nijmeh H, Linderman DJ, et al. Do more with less: tips and techniques for maximizing small biopsy and cytology specimens for molecular and ancillary testing: the University of Colorado experience. Arch Pathol Lab Med. 2016;140:1206–20. https://doi.org/10.5858/arpa.2016-0156-RA.

24. Xie M, Xu X, Fan Y. KRAS-mutant non-small cell lung cancer: an emerging promisingly treatable subgroup. Front Oncol. 2021;11. https://doi.org/10.3389/fonc.2021.672612.

25. Pennell NA, Mutebi A, Zhou Z-Y, Ricculli ML, Tang W, Wang H, et al. Economic impact of next-generation sequencing versus single-gene testing to detect genomic alterations in metastatic non-small-cell lung cancer using a decision analytic model. JCO Precis Oncol. 2019;3:1–9. https://pubmed.ncbi.nlm.nih.gov/35100695/.

26. Ciardiello F, Adams R, Tabernero J, Seufferlein T, Taieb J, Moiseyenko V, et al. Awareness, understanding, and adoption of precision medicine to deliver personalized treatment for patients with cancer: a multinational survey comparison of physicians and patients. Oncologist. 2016;21:292–300. https://doi.org/10.1634/theoncologist.2015-0279.

27. Hendriks LE, Kerr KM, Menis J, Mok TS, Nestle U, Passaro A, et al. Non-oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2023;34:358–76. https://doi.org/10.1016/j.annonc.2022.12.013. Cited 7 Feb 2023.

28. Rolfo C, Mack P, Scagliotti GV, Aggarwal C, Arcila ME, Barlesi F, et al. Liquid biopsy for advanced NSCLC: a consensus statement from the international association for the study of lung cancer. J Thorac Oncol. 2021;16:1647–62. https://pubmed.ncbi.nlm.nih.gov/34246791/.

29. Smeltzer MP, Wynes MW, Lantuejoul S, Soo R, Ramalingam SS, Varella-Garcia M, et al. The international association for the study of lung cancer global survey on molecular testing in lung cancer. J Thorac Oncol. 2020;15:1434–48. https://www.sciencedirect.com/science/article/pii/S155608642030383X.

30. Honoré N, Galot R, van Marcke C, Limaye N, Machiels J-P. Liquid biopsy to detect minimal residual disease: methodology and impact. Cancers (Basel). 2021;13:5364. https://www.mdpi.com/2072-6694/13/21/5364.

31. Robert NJ, Nwokeji ED, Espirito JL, Chen L, Karhade M, Evangelist MC, et al. Biomarker tissue journey among patients (pts) with untreated metastatic non-small cell lung cancer (mNSCLC) in the US Oncology Network community practices. J Clin Oncol. 2021;39:9004. https://doi.org/10.1200/JCO.2021.39.15_suppl.9004.

32. Waterhouse DM, Tseng W-Y, Espirito JL, Robert NJ. Understanding contemporary molecular biomarker testing rates and trends for metastatic NSCLC among community oncologists. Clin Lung Cancer. 2021;22:e901–10. https://doi.org/10.1016/j.cllc.2021.05.006.

33. Mileham KF, Schenkel C, Bruinooge SS, Freeman-Daily J, Basu Roy U, Moore A, et al. Defining comprehensive biomarker-related testing and treatment practices for advanced non-small-cell lung cancer: results of a survey of US oncologists. Cancer Med. 2022;11:530–8. https://doi.org/10.1002/cam4.4459.

34. Hsiao SJ, Sireci AN, Pendrick D, Freeman C, Fernandes H, Schwartz GK, et al. Clinical utilization, utility, and reimbursement for expanded genomic panel testing in adult oncology. JCO Precis Oncol. 2020;1038–48. https://doi.org/10.1200/PO.20.00048.

35. Socinski MA, Pennell NA, Davies KD. MET Exon 14 skipping mutations in non–small-cell lung cancer: an overview of biology, clinical outcomes, and testing considerations. JCO Precis Oncol. 2021;653–63. https://doi.org/10.1200/PO.20.00516.