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Advances in Minimally Invasive Screening for Lung Cancer: Breaking Data from Honolulu

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Welcome to CME on ReachMD. This activity, titled "Advances in Minimally Invasive Screening for Lung Cancer: Breaking Data from Honolulu" is provided by Prova Education. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Mazzone:
Lung cancer is the leading cause of cancer-related mortality in the United States; more people die every year of lung cancer than the next few cancer types combined. This is in part because it's very difficult to pick up lung cancer at an early stage. Despite lung cancer screening, with a low-dose CT scan being standard of care for the last 8 years or so, only around a quarter of everybody diagnosed with lung cancer in the United States is diagnosed at an early or localized stage. This is in part because of slow uptake of lung cancer screening, poor adherence to annual lung cancer screening, and concern about the management of all of the findings on the low-dose CT scan, mostly many benign lung nodules.

To help overcome some of these implementation challenges and find lung cancer earlier, there's a lot of great research being done on the development of molecular biomarkers, mostly blood tests that will help us to identify lung cancer early and work together with low-dose CT scan to optimize screening programs. When those blood tests are designed to help with lung cancer screening in those who are currently eligible for lung cancer screening, we want to make sure that those blood tests perform well. They're very sensitive; in other words, not missing a lot of lung cancers. And, their specificity might be a little bit lower; but a good specificity allows us to minimize how many people would have to go on to the low-dose CT scan.

So today, we're excited to discuss how molecular biomarker development is advancing early lung cancer detection, and in particular, review recent data presented in Honolulu at the CHEST annual meeting about two of these particular biomarkers. This is CME on ReachMD and I'm Dr. Peter Mazzone.

Dr. Barta:
And I'm Dr. Julie Barta.

Dr. Mazzone:
Julie, I wonder if we might start by talking a little bit about molecular biomarkers for early lung cancer detection. We often hear this term liquid biopsy; is molecular biomarker development for early lung cancer detection the same as liquid biopsy? What is liquid biopsy? And how should we think of these?

Dr. Barta:
Thanks, Peter. Let's start by distinguishing between liquid biopsy and molecular biomarkers for early detection. Liquid biopsy is a non-invasive way, usually through a blood-based test, to determine molecular features of a given tumor in someone who is known to have a cancer. And we can use liquid biopsy in a variety of clinical scenarios. So this can complement tissue diagnosis at the time of diagnosis to help characterize additional genetic alterations. It can be used to monitor treatment response, and it can also be used in surveillance potentially to predict relapse. But currently, liquid biopsy is not used for lung cancer screening or as a sole test for lung cancer

diagnosis.

In contrast, there's been a lot of work investigating molecular biomarkers for early detection. And in that setting, these types of biomarkers can be applied for risk assessment, or for cancer detection, specifically in asymptomatic individuals who are at risk for lung cancer.

Dr. Mazzone:
That's very helpful. And when I hear the word biopsy, I usually think, you know, something's there. We already know there's a nodule or mass, we have to sample it. We know there's a cancer, we need to biopsy it to help characterize it to decide on treatment. And that I think contrasts a little bit with what we're talking about today. And that's trying to identify individuals who might have an early lung cancer or who are at risk of developing an early lung cancer.

Can you, Julie, tell us just a little bit about these molecular biomarker strategies? You know, what sort of things are we looking for in the blood and why is this so important?

Dr. Barta:
Currently, there are several types of potential biomarkers for lung cancer detection that can be identified in peripheral blood, and then the data that are generated are typically analyzed using machine learning methods. And these assays may measure a variety of characteristics. And that can include mutations in circulating tumor DNA. It can measure circulating protein biomarkers. And assays can also measure DNA fragmentation patterns as well as DNA methylation patterns. And we'll focus a little bit later on this podcast about two studies investigating specifically DNA fragmentation and DNA methylation patterns.

I think from a clinical standpoint, this is a really exciting space because it has the potential to transform early detection of lung cancer, as you noted, Peter. You talked a little bit about low uptake of lung cancer screening among high-risk individuals. And in addition, we know that of patients who are diagnosed with lung cancer, only about 40 to 50% are actually eligible for lung cancer screening by current United States Preventive Services Task Force criteria. So I think there's a lot more that we have to learn about how to accurately characterize individuals who are at risk for lung cancer.

Dr. Mazzone:
Thank you, Julie. It's always fascinating to me as a clinical researcher and a clinician, when I see what is done in the lab with these markers. There are millions of fragments or millions of methylation changes. And then separating out, you know, which of those can help to predict the presence or absence of lung cancer using machine learning techniques and things of that nature is really, really fascinating and has come so far.

Dr. Barta:
I agree. And in particular, I think that the studies informing the abstracts that we'll discuss today are strong. As you know, DNA fragments are generated in apoptotic lung cancer cells, and then they get released into peripheral blood. So previous work has shown that these DNA fragments can have more variability in cancer patients, compared to a much more uniform or consistent fragmentation pattern in patients without cancer. Similarly, methylation patterns can also be different among patients with or without cancer. And specifically, hypermethylation, which is an epigenetic alteration, can lead to inhibition of tumor suppressor genes. So I look forward to hearing about how these can be applied in the clinical setting.

Dr. Mazzone:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Peter Mazzone in here with me today is Dr. Julie Barta. We're discussing advances in minimally invasive screening for lung cancer.

Dr. Mazzone:
Would you like to maybe jump into talking about these studies?

Dr. Barta:
Let's do that. So data from two studies were presented at CHEST 2023 in Honolulu in early October. Let's begin with the DELFI-L101 study. Can you tell us a little bit about that?

Dr. Mazzone:
Yeah, thank you. DELFI-L101 study was based on a classifier developed looking at fragmentation patterns in the blood, the fragmentomics that you just discussed. The work of developing this fragmentomics-based classifier started with a couple of proof-of-concept studies. In these proof-of-concept studies, you know, found samples were classified looking at millions and millions of fragments across the genome. And the ratio of small to long fragments in bundles across the genome was kind of the marker that the classifier was based on. Promising results from those studies led to the current study, which is a prospective case control study. So we enrolled individuals with cancer and without in the intended-use population. So this study was designed – this classifier is being designed to help improve uptake and adherence of lung cancer screening in those who are currently screen eligible. The study enrolled individuals who are currently screen eligible, who either had known lung cancer or did not have lung cancer. We enrolled around 958 individuals. The first 576 of these were used to train the classifier, at which point that classifier was locked down, no further changes to it were made. And on the remaining 342 individuals, the classifier was tested to see what its accuracy for detecting lung cancer in this group was.

Importantly, the group that was enrolled in this study was very similar in terms of their age and gender and comorbidities to those that are currently being screened today and those that had been screened as part of the National Lung Screening Trial. The only slight difference might have been a little bit lower percentage of individuals with stage I lung cancer.

The biomarker, the classifier that was developed and validated, performed quite with an overall sensitivity of around 80%; so 8 out of 10 cancers found. A little bit more sensitive in those with later stage disease, it performed fairly equally well in individuals regardless of whether it was a man or a woman, what their prior smoking history was, perhaps a little less specific in those who are a little bit older.

Overall, the accuracy was a sensitivity of 80% at a specificity of 53%. With that accuracy, if you had an individual who was eligible for screening, who was choosing not to get their CT scan, but they would if they – if they got that blood test done and had a positive result, you could tell them that if you have a positive result from this blood test, 1 out of 84 times you will have a lung cancer. And if you had a negative test result, 1 out of 381 times you would have a lung cancer. So, a helpful result clinically.

There's additional studies being done, other validation, prospective cohort studies being done to help confirm the accuracy. And then ultimately, clinical utility testing to make sure it actually helps as it suggested it would.

Dr. Barta:
Thanks for that detailed summary. We know that in the screening setting, that we need sensitivity to be at a relatively high level so that we don't miss lung cancers. And so, I think seeing that sensitivity in the study, that at 80%, is helpful. Although, as you pointed out, some high-risk subgroups may have a lower range of specificity.

Let's move on to the Sightline study. Can you tell us a little bit about that?

Dr. Mazzone:
Yes, another exciting study. This is a study looking at methylation patterns in cell-free DNA, that you had described. There were proof-of-concept studies as well, using these methylation patterns. And these were performed with methylation changes that were already known to exist based on prior literature. Promising results from those proof-of-concept studies led to a Lung Atlas being developed. And it was recognized that those methylation changes known in the literature were identified using a traditional means of looking at the methylone bisulfite sequencing. And that bisulfite sequencing, though good over time, it's not so sensitive to very low concentrations of methylation changes. So this Atlas was built using a different technique, methylation sensitive restriction endonucleases. And in using that approach, was able to find new methylation markers with 89% of the top methylation targets not previously found using bisulfite sequencing. This Atlas was also developed, in the intended-use population. So those who would be eligible for screening, and was heavily weighted towards early lung cancer stages, to help optimize the accuracy of that assay.

So in the study that we're talking about, the Sightline study, we're talking about the next phase, again, a prospective case control study, this time, the training and internal validation results, whereas the prior study, the DELFI-L101, was external validation. So one step prior to that. In Sightline, 813 individuals were enrolled. Again, they nicely matched those of the NLST [National Lung Screening Trial] in those beings screened today, with the possible exception of a slightly higher overall age. The cancer types that were included nicely matched the stage and histology of those in the National Lung Screening Trial. Using this methylation classifier in multiple machine learning algorithms, the top three algorithms were selected, and in the internal validation portion after training, the overall sensitivity of this assay was 90 to 92% with a sensitivity for stage I disease of around 87% and a specificity of 54 to 55%. These test accuracies were fairly

consistent across age, sex, comorbidities, and cancer histologies, with the possible exception of being slightly more sensitive in the older individuals and slightly less specific in that group.

The next steps for this classifier are to do the external validation and then to do a prospective cohort study to further validate those results, leading into clinical utility studies. But again, very, very exciting and promising results.

Dr. Barta:
Thank you for that summary, Dr. Mazzone. I agree the Sightline study has a lot of potentially impactful findings. And notably, again, we see some variable test performance across disease stage and among certain high-risk subgroups.

Dr. Mazzone:
Thank you very much for that perspective. And with that, all that's left for me to do is to thank our audience for listening in and to thank Dr. Barta for joining me. It was great speaking with you today.

Dr. Barta:
Thanks for having me, Dr. Mazzone. Take care.

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