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ReachMD
www.reachmd.com
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(866) 423-7849

Optimizing NSCLC Care: Advances in Lung Biopsy and Biomarker Testing

Announcer:
You're listening to *Deep Breaths: Updates from CHEST* on ReachMD. This program is produced in partnership with the American College of Chest Physicians and is sponsored by AstraZeneca. And now, here's your host, Dr. Gerard Silvestri.

Dr. Silvestri:
This is *Deep Breaths: Updates from CHEST* on ReachMD. I'm Dr. Gerard Silvestri, a pulmonologist and the Hillenbrand Professor of Thoracic Oncology at the Medical University of South Carolina. Joining me today to discuss our evolving approach to biopsy and biomarker testing in non-small cell lung cancer are Drs. Fabien Maldonado and Adam Fox.

Dr. Maldonado is a Professor of Medicine and Thoracic Surgery, the Pierre Massion Director in Lung Cancer Research, and the Director of Interventional Pulmonology Research at Vanderbilt University in Nashville.

Dr. Maldonado, welcome to the program.

Dr. Maldonado:
Thank you for having me.

Dr. Silvestri:
Also joining us is Dr. Adam Fox, who's a pulmonologist and Assistant Professor of Medicine at the Medical University of South Carolina in Charleston.

Dr. Fox, it's great to have you with us as well.

Dr. Fox:
Hey, Gerard. Thanks for having me on.

Dr. Silvestri:
For the first half of our program, I'd like to focus on recent advances in lung biopsy with Dr. Fabien Maldonado.

So, Fabien, we've seen unprecedented technological advances in lung biopsy over the past five years. But do these innovations actually improve outcomes?

Dr. Maldonado:
Thanks, Gerard. I think that's a great question. We've seen a plethora of new technological advances over the past decade or so with robots, different biopsy tools, like cryobiopsy, ablation devices, and therapeutic devices for lung cancer. And what's important to understand is that most of these devices have been introduced on the market with clear evidence of improved patient outcomes. And I think we need to understand why that's the case. Devices, at least in the US, tend to be introduced in the market through the 510(k) pathway, which is a pathway that allows commercialization of devices based on their "substantial equivalence" to pre-existing so-called "predicate devices."

And so what's happened in practice is that the burden of producing quality data and showing improved patient outcomes has shifted to clinicians, who traditionally have been very busy and not necessarily research trained. And the kind of studies that we've had over the past decades have been predominantly observational, noncomparative studies with all the biases and limitations inherent in these types of study designs.

You had a wonderful meta-analysis with over 120 studies and 16,000 lesions, showing that, in essence, the diagnostic yield before 2012

and after 2012 had not shifted significantly. And I think the study was interesting in many respects, but one great question about this study is why that would be the case. I think there are two possible explanations for this. One is that it truly indicated we haven't made any progress, and we have not improved patient outcome. The second possibility is that we're going after more difficult lesions.

And I think the lesson for this study for many of us was that we really need to pay attention to the way these studies were designed, and that led us to two important realizations. One is that we're measuring success in these studies in many different ways, and so a very important outcome of these reflections was the consensus statement that CHEST and the ATS produced to harmonize diagnostic yield—specifically strict diagnostic yield—as the primary outcome, which is a patient-centered outcome. It's a validated endpoint, and it's also an endpoint that can be adjudicated fairly quickly during the study, which is important.

The other realization is that, when we look at the success or the improvement in patient outcome from these platforms, what we're looking at is not a single platform, but a plethora of other things that go along with the platform: how good you are as a proceduralist, how good your pathologists are, and whether you have access to ROSE, radio ultrasound, and a variety of other things. And we realized that in order to adjust for all these possible confounders, we needed clinical trials—specifically randomized clinical trials—that can account for all known and unknown confounders. And so we started this process many years ago with VERITAS that was just recently published and set the standard for the way these clinical trials should be done. We showed that we could reach diagnostic yield estimates with bronchoscopy that are on par with the traditional gold standard of CTA biopsy with less complications for patients.

What we've also realized is that these studies take a lot of time and a lot of funding. and we need to do them in an easier and more expeditious way. And that's what led us to consider more pragmatic study designs with, for example, RELIANT, RELIANT2, FROSTBITE, and number of other studies that we are conducting now. So I think the future is bright for clinical research in bronchoscopy and lung biopsy, and we're really excited to be moving this field forward.

Dr. Silvestri:
I want to take a moment to compliment you and your team and others on the VERITAS trial, which was published recently in the *New England Journal of Medicine*. And you alluded a little bit to that, which is to say that one of the things that this field has sorely needed is comparative effectiveness trials. And this was a randomized trial looking at CT-guided biopsy and/or guided bronchoscopy, showing that they were essentially equivalent from a diagnostic yield standpoint. That's one thing. The second thing was that it showed that the CT guided biopsy, which we'd always quoted 90-plus percent in terms of yield was actually closer to 80 rather than 90. And then the third is that the complication rate was lower.

Do you think that doing that level of trial is now going to translate into other comparative effectiveness trials going forward?

Dr. Maldonado:
I think it has already. And as you know, Gerard, it took forever to get this study going. We got the grant in 2018 and we published the results just a few months ago. In that interval of time, the whole landscape of bronchoscopic lung biopsy has changed. When we started with VERITAS, there were no robots on the horizon, and now we've got three different robotic platforms and a variety of new technologies to assess.

And that really pushed us toward considering more pragmatic clinical study design. And what do I mean by that? Pragmatic study designs are often misunderstood, but the basic component of a primary clinical trial is we include everybody. We want to be as generalizable as possible. We prioritize external validity over internal validity—still trying to be methodologically rigorous, obviously. We want to embed these clinical trials in clinical care to avoid burdening clinicians who are already very busy with a lot of research activities that would be not conducive to expeditious generation of data. We want to be flexible with co-interventions. We want people to practice the way they usually practice and not describe every single minute detail of the procedure. And finally, we want outcomes that are patient-centered, and that's where this diagnostic yield outcome is so important. I know that's a somewhat controversial topic, but in reality, that's what patients want to know: did you get what you needed to get to inform my care? And that's why this diagnostic yield is important.

So, we have a number of pragmatic clinical trials, like RELIANT, which was just published in the *Blue Journal* comparing robotic bronchoscopy to electromagnetic navigation bronchoscopy. We have RELIANT2—that's already more than half accrued. And then we're moving into biomarkers too, which is really interesting.

We have a study that's all unfunded right now called the SPOTTED trial, which is looking at adjunct radiomic imaging for the adjudication of lung nodules before the biopsy because the goal here is ultimately to do away with invasive procedures that are associated with complications.

Dr. Silvestri:

I've seen this easing its way into the literature—this triple goal of lung biopsy, diagnosis staging, and molecular profiling. So do you think that's going to become the standard—you go out with whatever platform you use and try to get to the lesion itself and then do a full mediastinal node staging and molecular markers if they're available—do you see that as a laudable goal in a single procedure?

Dr. Maldonado:
Yeah, I think it's the goal now, right? We've been talking about this for some time, and we're not pure technicians. We've graduated to become true partners in the multidisciplinary approach to lung cancer diagnosis and even treatment. We're "onco-pulmonologists." We are often the point of entry for patients in their lung cancer journey. We have to think from the end. What could this be? Could this be cancer? And if it is, what kind of stage is it?

And so that prompts us to not just get the diagnosis and be out of there operating in silos, but getting the diagnosis, getting the proper staging, and getting enough material in quantity and quality to get the next-generation sequencing patients need for their treatment. But also, orchestrating the whole care of the patient—we order the PET scan and the brain MRI. We might order the NGS that Adam will talk about in a little bit. And we are there with patients along their journey.

Dr. Silvestri:
Thank you so much. For those just tuning in, you're listening to *Deep Breaths: Updates from CHEST* on ReachMD. I'm Dr. Gerard Silvestri, and I'm speaking with Drs. Fabien Maldonado and Adam Fox about how we can improve biopsy quality and biomarker testing in non-small cell lung cancer.

So in the first half of our discussion, we explored the latest biopsy innovations with Dr. Maldonado, but now I'd like to shift our focus toward biomarker testing with Dr. Adam Fox.

So, Adam, why is timely biomarker testing so important in early stage, non-small cell lung cancer? I think we've all seen that it's important for metastatic disease, but why has it moved backwards towards earlier stage disease?

Dr. Fox:
That's a fantastic question, Gerard. Upfront biomarker testing has become critical to determine first-line treatments for most patients newly diagnosed with lung cancers—especially those who have tumors that are four centimeters or greater or who have any lymph nodes involved. So, if a patient does have resectable disease, it really determines whether the patient may be eligible for a neoadjuvant therapy like chemoimmunotherapy or an adjuvant targeted therapy. And so, it even determines who you should be referring the patient to in some regard. Does the patient really need a surgeon and need to get a surgery as soon as possible? Or do they also need to see a medical oncologist to see if they're fit enough for chemo and immunotherapy as well? These biomarkers determine the first optimal treatment, and that's why it's so important.

Even for patients with unresectable disease, it's still critical for basically the same decision point. Should they be choosing one of these other systemic therapies guided by biomarkers? And if their initial therapy is unsuccessful at cure and they do have progression of disease or recurrence, those same biomarker tests are likely to inform the next line of treatment for them at that point, too.

Dr. Silvestri:
If you're doing a bronchoscopy, and want to do molecular testing, how many passes of the lymph node do you take after you know it's cancer, or altogether?

Dr. Fox:
We do have rapid on-site evaluation at our bronchoscopy suite, and we do take the feedback from the pathologists and the cytotechnologists on the cellularity of the samples they're seeing so far. But we think that the right number is somewhere closer to six to seven or more, especially for the cell block beyond the diagnostic tissue. The old adage was three passes for a diagnosis, and we think that many more like six dedicated passes or more is more beneficial. That does depend on the assay that you're using, and so a little bit of awareness of the types of specimens that are required and acceptable by the lab is important knowledge for pulmonologists now.

Dr. Silvestri:
So, as a follow up to that, what are some of the practical ways a pulmonologist can help ensure prompt and efficient biomarker testing?

Dr. Fox:
I would say the quintessential step here is communication. I would really challenge pulmonologists not to assume that just because they've not heard anything that biomarker testing is being performed effectively and efficiently on all their samples. I would challenge them to talk to their colleagues, pathologists, oncologists and surgeons about sample adequacy. So are they taking enough passes? Is their success rate fairly high? And also, ask about the timeliness of testing. As some of the survey work that you and I have published in *CHEST* has shown, there's variability not only in practices for ordering by pulmonologists, but also in their knowledge of how testing is

performed within their kind of network or institution. So some institutions do have streamlined care via reflex testing, and that could be ordered by a designated staff person, or pathology-driven where the pathologist orders at the time of diagnosis.

But based off our previous work, Gerard, some people simply do not know how testing is completed. So the first step, I think, is a conversation with your multidisciplinary team or referral network.

Dr. Silvestri:
I think most people would be surprised if they started following their own biopsies—how long that time from when the biopsy is taken to a final readout from the NGS testing is done. And you and I have looked into that, and it's really a long time between when the biopsy is taken and the order for biomarker testing is actually written. And that variability can be up to 14 days before it's even sent out or done in-house. And so I agree with you completely—communication is the key.

As we approach the end of our program, I'd like to bring both guests back together and ask each of them to share a key takeaway point from our discussion. Dr. Maldonado, care to start us off?

Dr. Maldonado:
I enjoyed the conversation very much. I would say that as technology evolves and NGS assays evolve as well, we're probably going to change our practice, and we'll have strong data to guide this. We have the FROSTBITE3 study right now, which is looking at cryobiology for NGS. We have no idea whether this helps or not, but doing the study is certainly an important thing.

I would just reiterate what I just said—the pulmonologists doing bronchoscopy and lung biopsies have really become the quarterback of the team. We see more and more pulmonologists involved as leaders of the tumor board and orchestrating the care of patients from beginning to end, and I think that's a positive development for patient care.

Dr. Silvestri:
And Dr. Fox, I'll give you the final word.

Dr. Fox:
Well, I'd like to jump on what Dr. Maldonado just said, which is pulmonologists should be poised to really help with biomarker testing. And if we take a patient-centered approach here, as Dr. Maldonado did earlier, patients don't care who orders their biomarker testing. They only care about a fast, effective treatment for their cancer. And so if we take that perspective, we have to look at our individual group in our own systems and referral networks and say, “How can we all come together to get this stuff ordered for patients?” So, I really have enjoyed the discussion, too, and thank you.

Dr. Silvestri:
I would say that, from research where we actually assess patient-centered outcomes, like how many salvage procedures they have and how long it took to time-to-treatment, those are important outcomes from the research side. But they're equally important, as you mentioned, Adam, from the patient side. The most stressful time for a patient is the time between that they’re told they might have cancer and the time to their first treatment. That’s psychologically the most damaging time for a patient. We could certainly do better—all of us—in that regard.

As those insights bring us to the end of today's program, I want to thank my guests, Fabien Maldonado and Adam Fox, for joining me to discuss biopsy and biomarker testing in early-stage non-small cell lung cancer. Thank you both for being here.

Dr. Maldonado:
Thank you for having me.

Dr. Fox:
Thanks for having me on.

Announcer:
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