MoIDX October Open Meeting Transcript

October 9, 2023, 4:01PM

1h 1m 57s

C **Dr. Angella Charnot-Katsikas** 0:09

This is Dr. Angela Charnot-Katsikas and I am re announcing that we have just started the recording of this open meeting and compliance with CMS for the recording prior to doing so, I announced that Palmetto GBA would make an audio recording of the open meeting and consented on behalf of Palmetto GBA.

So welcome everyone again to our MolDX Open meeting.

We're going to jump right in.

We have 5 speakers today and our first speaker is Doctor Ashley Ross, associate professor of Neurology, and she or he will be talking about gene expression profile tests for decision making in castration, resistant and metastatic prostate cancers.

RA **Dr. Ross, Ashley** 1:03

Thank.

Thank you very much.

And again as mentioned, I'm doctor Ashley Ross.

I'm gonna associate professor of urology at Northwestern Feinberg School of Medicine in Chicago, where also direct the Polsky.

You're a logical oncology institute.

RA **Dr. Ross, Ashley** 1:16

I'm very happy to be speaking about gene expression profiling in metastatic prostate cancer.

Specifically, the decipher test by variscite.

My practice focuses pretty much exclusively on prostate cancer.

And my career has focused on the development of novel technologies for the diagnosis, risk stratification, and treatment of the disease.

I've been able to collaborate with a lot of different biotech companies towards those ends leading to money products that are used by our patients on a daily basis and various site is one of those companies and I'm going to be talking about their product today.

So, as many of you are aware, prostate cancer is the most common non-skin cancer among American men and the second most lethal cancer among American men.

RA **Dr. Ross, Ashley** 2:06
In my practice, I've seen the incidence of metastatic prostate cancer increase over time and that is recapitulated in the data we have about the incidence of prostate cancer in America.

RA **Dr. Ross, Ashley** 2:20
If we look at the left and we look at prostate cancers diagnosed over time, the red line that I'm pointing to here is metastatic prostate cancer and that incidence has increased over time and much of that increase has been in the older population shown here on the right, the incidents of metastatic disease and locally advanced disease has been increasing, particularly in older men when men present with metastatic prostate cancer, they can have multiple different presentations and those presentations can somewhat dictate their outcomes, the ways they present or shown here on the left, some individuals will be diagnosed in the localized setting where we can treat their prostate cancer.

RA **Dr. Ross, Ashley** 3:05
But later we'll have progression of disease and have metastatic sites found other individuals present for the first time with metastatic disease, either with a few sites of metastasis around their body called low volume metastatic disease, or multiple sites of metastasis throughout their body.
We call this high-volume metastatic disease and how they present can affect their overall outcomes.

RA **Dr. Ross, Ashley** 3:29
If you look to the right here, we can see the median overall survival for men presenting in these different settings, some of them with lower volume disease that have had prior treatment, can have a meeting.
Overall survival of eight years and it can be as little as three years for men with high volume, newly presenting metastatic disease and maybe paralleling that.
There are a lot of different treatment options that societies like the National Comprehensive Cancer Network present to us as clinicians for these patients with

metastatic prostate cancer, all of them have as their backbone a deprivation of testosterone, which has been known for over for about a century, to reduce the morbidity and deaths from prostate cancer.
But then there can be intensification with other agents that block the antigen receptor or with agents like chemotherapy.

RA **Dr. Ross, Ashley** 4:22
And here's some of the data that led to this.
This is one of the larger trials, called Stampede, that compared blocking testosterone alone to blocking testosterone and blocking androgen production from things like the adrenal glands, with an oral agent called abiraterone, and what you can see here on the left in the survival curves for these metastatic men is that if the combination therapy was used compared to blocking testosterone alone, you've got about a 10% survival overall survival benefit that four years now, though, it's a subset analysis, the forest plots to the right and highlighted here in the red show us that not all men necessarily will benefit from intensification of therapy if we specifically look at the area of the group of men who are 70 year olds or older, which is this group here, the additional survival benefit from adding abiraterone was basically negligible

RA **Dr. Ross, Ashley** 5:23
So this brings the question forth of how do we decide between these multiple treatment strategies proposed as different standards of care.

RA **Dr. Ross, Ashley** 5:32
If we over treat the individual, we may decrease their quality of life due to therapeutics that increase morbidity.
We will also increase cost to that patient and increase the financial toxicity to the medical system if we under treat that patient, we may decrease their quality of life due to the disease progression and that causing disease related morbidity and mortality and possibly by choosing the wrong initial therapeutic option, we will need more intensification and more therapies down the road which can increase cost and a lot of this is going to be dependent on the risk stratification of the tumor.

RA **Dr. Ross, Ashley** 6:12
It's how the patient presents how their how their Physiology is and health is and what

is the biological characteristics of the tumor.
And in prostate cancer, we've done a lot to increase our understanding of tumor biology.
A lot of that has come through genomic gene expression based testing, particularly the decipher genomic classifier that we're talking about in this in this talk.
Now this is a gene expression signature that looks across seven different cancer pathways and reports a score based on a 22 gene signature.
That gene signature has been heavily validated as a predictor of overall survival and prostate cancer specific survival.
It's been looked at in about a dozen randomized phase three trials where it's looked at retrospectively, including several trials in the metastatic setting, and it's also been looked at in real world evidence, including in around 8000 patients from NCIC.

RA **Dr. Ross, Ashley** 7:13
Here and in a clear of eight and a clear of eight real world registry of about 90,000 patients.
So let's look at that data around decipher in the metastatic setting.
This comes from the patience of the Stampede trial.
What you can see is that if you understand the tumor biology using the decipher score and that's based on routinely collected pathologic tissue, then even if you adjust for the age of the patient, the volume of their metastatic disease, their PSA and other factors, the decipher genomic classifier still has prognostic significance for important outcomes like overall survival, prostate cancer, specific survival and progression free survival.

RA **Dr. Ross, Ashley** 8:04
Let's look at that in a different type of representation.
This is the Stampede population of metastatic men.
On the left you can see their survival curves for men's stratified by having decipher scores above the median shown in red or below.

RA **Dr. Ross, Ashley** 8:21
The median shown in green and then further substrata fried by the treatment they got the solid lines showing therapy with just testosterone, block production, blockade and the dotted lines.

I'm sorry the dotted lines showing that and the solid lines showing a combination therapy of testosterone blockade and abiraterone on the right here, you can see the absolute benefit in overall survival by intensifying therapy in which you can note is if the genomic classifier is higher than the median shown in red therapeutic intensification, for example, at three years is about a 35% overall survival benefit, but only about a 2% benefit for men with lower genomic classifier scores.
There are tumors being less biologically aggressive.
So it's my hope that we'll have an extended indication for the decipher genomic classifier and I can bring it to my patients with metastatic prostate cancer.
And I hope that you've seen how I might use this data to guide my care of my patients.
This, quite simply, we can look at their genomic potential of their tumors from a lower risk to higher risk.
And we can look at other patient factors and decide on their therapeutic regimen in the metastatic setting, a patient who might have lower burden of disease and more limited life expectancy with a lower genomic score might do quite well with hormonal therapy 80T, which is Energen depression as a monotherapy and that could save them a lot of morbidity, both personal morbidity and financial morbidity.
Whereas a patient who has a higher volume of metastatic disease who's perhaps more fit with a longer overall survival projectory may benefit from therapeutic intensification with multiple agents and there may be patients that fall somewhere in between.
I'm going to stop there and take any questions.
I tried to leave a few minutes for that.

C **Dr. Angella Charnot-Katsikas** 10:33
Thank you, Doctor, but we actually do not have time for questions.
Any comments should definitely be submitted in writing during this comment period, so thank you for your presentation.

RA **Dr. Ross, Ashley** 10:40
Umm no problem.
Thank you.

C **Dr. Angella Charnot-Katsikas 10:55**

Next we have Doctor Billatos, assistant professor of medicine, who will be speaking on molecular biomarkers for risk stratification of indeterminate pulmonary nodules following bronchoscopy.
It looks like some others have shared their screens, so if you could not share your screen so that doctor Billatos can share the screen and begin the presentation.

BE **Dr. Billatos, Ehab** 11:42
Yes.
Can you guys hear me?

C **Dr. Angella Charnot-Katsikas** 11:45
Yes, we can.
And anyone who is not presenting please if you have inadvertently shared your screen, stop sharing.

C **Dr. Angella Charnot-Katsikas** 11:54
OK.
So Doctor Billatos, we can see you go ahead and share your slides please.

BE **Dr. Billatos, Ehab** 12:00
Scale one moment just opening up Madison technical difficulties.
But I'm opening up the slides right now.

BE **Dr. Billatos, Ehab** 12:33
Sorry about that.

C **Dr. Angella Charnot-Katsikas** 12:54
We did see your screen a moment ago.
Just wasn't on the PowerPoint slide.

BE **Dr. Billatos, Ehab** 12:59
Yep, OK.

C **Dr. Angella Charnot-Katsikas** 13:02
So whatever you did before and try again.

Dr. Billatos, Ehab 13:04

It was.

It was working.

Yes, that's right.

Just a moment here.

Dr. Angella Charnot-Katsikas 13:27

OK, we see your screen.

So now we're just need to, there we go.

We see your slides.

They're not in slide show mode, but we do see them.

Dr. Billatos, Ehab 13:38

OK, let me see.

Alright, sorry.

Just one more moment that I could just fix.

One quick thing about this before we move on.

OK.

Dr. Billatos, Ehab 14:53

How you guys can see slides now, is that right?

Dr. Angella Charnot-Katsikas 14:55

Yes, we see them.

Billatos, Ehab 14:57

Perfect, very good.

Let's see here.

Hi.

So thank you for giving me the opportunity to present regarding the local coverage determination for a molecular diagnostic in the setting of indeterminate pulmonary nodules.

Just to introduce myself, my name is Ehab Billatos.

I am a pulmonologist and an assistant professor of medicine at Boston University.

I have a couple of roles in the director of inpatient clinical Services and the director of bronchoscopy, so I oversee the bronchoscopy training for our fellows as well as some of our more advanced bronchoscopic techniques for lung cancer diagnostic.
And perhaps maybe most relevant that to the topic at hand today is that I run our lung cancer screening program with an active and fairly busy lung nodule clinic that has a physicians, nurse practitioners and a couple of patient navigators that sees over somewhere around 2000 lung nodule patients a year.
My clinical focus is mainly in lung cancer as well as my research focus where our labs specializes in bioinformatics and using computational approaches to developing lung cancer diagnostics.
So lung cancer, as many of you may know, as the leading worldwide cause of cancer mortality.
And there were, I think, an estimated 2.2 million cases of lung cancer diagnosed last year and 1.8 million deaths from lung cancer globally.
And so combine that makes lung cancer the second most common cancer diagnosed worldwide after breast cancer.
And by far the mostly most lethal cancer, accounting for almost 20% of all cancer deaths, now a major contributor to the sort of lethality of lung cancer, is that most lame lung cancers are diagnosed at an already advanced stage.
Maybe only 15% of lung cancers or so are diagnosed at stage one.
All over 50% of lung cancers are diagnosed when there's already distant metastases.
So you got a 5 year mortality of stage four disease being somewhere around 5 to 10%.
To that end, the focus within the field has been on trying to move the needle and advance diagnosis, shifting more patients from late stage disease into early stage disease and screening for lung cancer was generally not considered.
That's successful until 2011, when the NLST demonstrated a reduction among cancer mortality, 20% using low dose CT screening of a selected pool of high risk patients.
And so as a result is, you know, lung cancer screening is the standard of care in the US and many other countries now, although the trial is a success, the screening protocol have produced the high number of false positive results with maybe 1/4 scans or so coming back as positive and maybe 6% of those is transitive.
How in in 2015?
Umm.
Publication that that came out that showed that there was an estimated 1.6 million

indeterminate pulmonary nodules that were identified through this process.
And that number is likely higher now due to more people getting regular lung cancer screening, but also with broader screening criteria.
In addition to lung nodules being identified, identified via lung cancer screening, so you T is we also see uh that there are other avenues by which the patient may be identified with a lung nodule.
It could be, incidentally, at a patient that's undergoing a CT for some other reason, and we actually see this fairly often for patients who presents the emergency room for some other condition, maybe to have chest pain, and they're found to have a pulmonary embolism, for example, or there are other cases where they have symptoms that are red flags remotely and see such as hemoptysis or unexplained weight loss.
But regardless, it all that means just that, that, that 1.6 billion nodules and that I mentioned earlier, probably underestimates the true number of modules that we see as a, as a medical community.
So how do we manage all those lung nodules?
It really comes down to risk stratification.
You know, once a nodule is identified, the clinician has to make a decision either to pursue further diagnostic workups such as a PET scan or tissue sampling via bronchoscopy or a transthoracic needle aspiration, or sometimes even straight to surgical resection.

BE **Dr. Billatos, Ehab** 19:23
Or they can opt for surgical survey.
Sorry, they can opt for surveillance imaging of the nodule to ensure the stability.
Now that decision is primarily driven by risk assessment.
So high risk module will go down the more aggressive management pathway of invasive work up while a low risk module can follow conservative management.
But the problem is that that decision is rarely easy and I can speak as a physician on sort of the brunt end of, you know, 1.6 million nodules a year and that, you know, we need help instead of do I think I need help instead of many others that are in the field.
There's this clinically unmet need to help the provider make the decision of whether a patient needs invasive procedures versus non-invasive monitoring and a biomarker in this space would be particularly useful to addressing that clinically unmet need.

CMS is in the process of finalizing the local coverage determination from molecular biomarkers for risk stratification of indeterminate pulmonary nodules and LCD that I'm particularly excited about given how relevant this is to my practice and to millions of patients in the US.
However, the language of the current LCD I think limits this coverage to post bronchoscopy, but that doesn't quite align with the current paradigm of nodule management.
Bronchoscopy is still part of the invasive diagnostic work up arm and any biomarker in this space should really be designed to help us make that determination before bronchoscopy.
Why?
Well, bronchoscopy like any procedure in the hospital, carries with it some inherent risks to the patient, you know, and it's a decision that we don't take lightly.
And as such, we wanna avoid unnecessary bronchoscopies and patients who don't need it at the same time, there are a subset of patients whose risk, as determined by this risk classifier or by any risk classifier could be so high they could bypass a diagnostic procedure altogether and proceed directly to surgery.
And either case, a risk classifier ahead of or before bronchoscopy helps to open up these pathways.
And really better align with current clinical practice.
Now I know that there are a number of classifiers already in development and most if not all are designed in the pre bronchoscopy or pre procedure setting.
So whether it's blood based biomarkers from companies like Biodesix or lung life AI or nasal gene expression, biomarker from companies like varsity, the goal remains the same.
It's really to risk stratify patients who have an indeterminate pulmonary nodule before they require any further testing, like bronchoscopy.
I'll speak briefly on the nasal gene expression classifier.
Just says as an example of such a test that meets that clinically unmet need.
Although any of these tests could sort of be discussed in this in this setting, so our lab that Boston University has primarily focused on a promising approach that uses gene expression profiling of the relatively accessible airway epithelium as a window for sampling carcinogen exposed tissue that we believe that have shown could reflect the molecular signatures of cancer associated processes.
This concept or this idea that you could detect molecular alterations and epithelial

cells throughout the respiratory tract that are exposed to carcinogens is called the field of injury.
How we first discovered this from airway epithelial cells that were obtained via bronchial brushings in patients who have been exposed to cigarette smoke, and we demonstrated that by studying these gene expression patterns there is a detectable physiologic response to tobacco smoke that occurs commonly immediately and largely reversibly.
Individuals who smoke now, perhaps more interestingly, and maybe more relevant to the topic at hand, is that some of these changes persist over time.
In other words, they are irreversible, even in those who quit smoking, which we believe can first some sort of increased risk of lung cancer development in the future.
And from there, our labs ought to study other, quote unquote injuries to the lung, specifically lung cancer and under a similar yet distinct paradigm of field cancer Azatian.
We hypothesize that a tumor that's buried deep in the lung would exert its effect on other cells.
Specifically, cells in the airway epithelium that are easier to sample than the tumor itself, and to that end we studied airway up aphelion cells from bronchial brushings to illustrator.
Relationship between the molecular changes that are present in the airway epithelium and those that are present in the tumor, and when these molecular changes happen reliably and predictably and you have the basis for molecular biomarker, something that uses, you know, less invasive tissue sampling for lung cancer detection that's remote to the actual tumor.
So we published and refined and ultimately validated a bronchial classifier using two large multicenter clinical cohorts of current and former smokers undergoing bronchoscopy for suspect lung cancer.
Just called Egis one and Egis 2, and these studies collected pre diagnostic bronchial epithelial cells from the mainstem bronchus and then follow patients until a final diagnosis was obtained.
And ultimately, we demonstrated that the combination of bronchoscopy with this gene expression classifier performed pretty well, 97% sensitivity as compared to bronchoscopy alone, which was 75% sensitivity.
And more specifically, we found that in the subset of patients whose bronchoscopy was inconclusive, and the pretest probability that was assigned by the physician was

intermediate.
We demonstrated an 88% sensitivity and 91% negative predictive value and that genomic classifier that was developed and validated in the Egis trials has since been commercialized as the Percepta bronchial genomic classifier, which is a clear based 23 gene genomic classifier, but for the reasons that I outlined earlier, a bronchial genomic classifier is really limited in its scope and practice.
You know, there's been more of a push to find less invasive options for lung cancer detection and risk classification, something that can be used upstream, a bronchoscopy and really limit the associated procedural risks to those patients on only those patients who truly need it.

BE **Dr. Billatos, Ehab** 25:46
And so if we believe that cancer exerts a field of injury on the airway epithelial cells, well then how far up the airway can you go?
Perhaps the trachea, instead of the mainstem bronchus, or perhaps the larynx, or even as far as the nasal epithelium.
Any of these could be options, given that we believe the field is detectable in any of these places, but the idea of a nasal epithelial bar biomarker has real implications for management based on its ease of acquisition and a scaling for widespread indications.
So first as a proof of concept, we wanted to at least see if the same gene expression changes from the Broncos.
You know the ones that we have validated in these two large multicenter prospective trials could be replicated in the nasal epithelium, OK, we were able to show that the changes in the nasal epithelium do info do in fact reflect the same changes that are seen in the bronchial epithelium.
And this was then further developed as a as a discovery biomarker from a training set of about 1100 patients analyzing the gene expression from brushings at the nasal epithelium and then a few other clinical factors.
You know, age pack years, years since quit, and a couple of nodules, specific features like the size and speculation.
And it was finally validated in 250 patients collected from a number of different cohorts and the performance metrics that I'm showing here demonstrate that the negative predictive value in patients with the test identified as low risk was 98%, while the positive predictive value in patients at the test identified as high risk with

70%.
And that was really exciting, I think to see showing not only the classifiers ability to function as a rule out with a high negative predictive value, but also assist as a rule in for those patients with intermediate risk, Greek test probability and so those patients that have that higher pretest probability or the OR the higher risk that's assigned by the classifier, maybe ones that we can then select for further testing whether it be tissue sampling via bronchoscopy or tissue sampling with a transthoracic needle aspirate or even to go straight to surgery.
So sort of to conclude what I want to say is that, you know, I'm very excited with the directions and advances that we as a medical and scientific community have made in the last few years.
And I hope that some of the discussion here is help give my perspective as a physician that sees lung nodule patients on a daily basis to shed some light on the clinically unmet need for lung cancer diagnosis diagnostics and how biomarkers that assist the physician with risk assessment prior to any bronchoscopy or other invasive diagnostic tests.
How that sits in the paradigm of lung nodule management and thank you for your time.

C **Dr. Angella Charnot-Katsikas** 28:37
Thank you for your presentation.
With that, we will move on to our next speaker, Doctor Paul Ladenson will speak on molecular testing for risk stratification of thyroid nodules.
And we do see your slides.

C **Dr. Angella Charnot-Katsikas** 29:10
It's actually late in send you may be on mute.

PL **Paul W. Ladenson** 29:18
Thank you.
Umm I'm Paul Ladenson, a professor at Johns Hopkins University School of Medicine.
Where in the roles you see described on this slide I on a regular basis evaluate patients with the common problem of thyroid nodules, an issue detected in anywhere from 5 to 50% of adults.
Uh, I perform fine, needle aspiration biopsies and A and a participant in decision

making about the use of molecular testing for thyroid nodules proving to be subtle, logically benign.
Ohh what I and other clinicians involved in the care and evaluation of patients with thyroid nodules need and value.

C **Dr. Angella Charnot-Katsikas** 30:30
It looks like you may be on mute again.

PL **Paul W. Ladenson** 30:35
I'm sorry.
Umm.
Uh, in that role, what I and other clinicians are looking for and value in a thyroid nodule, molecular test is the opportunity to avoid unnecessary thyroid surgery or procedure carried out in more than 90,000 Americans annually.
Ohh, we need a reliable test to rule out a thyroid malignancy.
We need a test that.

C **Dr. Angella Charnot-Katsikas** 31:10
And doctor?
Doctor Ladenson, we no longer see your slides on the screen.

PL **Paul W. Ladenson** 31:21
Let me share again.
Have they returned?

C **c2401652-10ce-4bb3-ae41-539e1f50b273** 31:30
They have not.

PL **Paul W. Ladenson** 31:32
Alright.
And now?

C **Dr. Angella Charnot-Katsikas** 31:46
They have not, no.
And if anyone else is trying to share, please make sure you are not sharing.

We only want the presenters.
There we go.
Perfect.

Paul W. Ladenson 31:57
Yeah.

Dr. Angella Charnot-Katsikas 31:57
We see them.

Paul W. Ladenson 31:58
So what I and other conditions involved in the care of thyroid nodule patients are looking for is a chance to avoid unnecessary thyroid surgery.
We want confidence that malignancy will not be missed by these tests, which currently offer a sensitivity for detection of cancer in excess of 95% and as confidence in the accuracy of these tests and not only their diagnostic but also prognostic potential has grown

Paul W. Ladenson 32:36
We are looking for a guide to the optimal approach to therapy in these pre surgical patients based on the extensive panel of mutations and molecular information available preoperatively in their biopsies.
The first request that I have today is really a request for a clarification.
It's a request for the approval.

Dr. Angella Charnot-Katsikas 33:12
I talk.
I sorry, doctor Ladenson.
We again lost your slides.

Paul W. Ladenson 33:18
I don't know what's happening here, but we'll get them back.

Dr. Angella Charnot-Katsikas 33:22

If, if you are alright and then if this happens again, perhaps someone from our team can take over and then share.

Dr. Angella Charnot-Katsikas 33:29
But we do see them, they're back.

Paul W. Ladenson 33:31
Right.
So the first request is one for clarification of the need for potential molecular testing on more than one thyroid nodule in the gland of the 30% or so of patients with thyroid nodules who have multinodular goiters the opportunity to perform molecular testing on any Bethesda 3-4 indeterminate nodule could change the optimal treatment choice.

Dr. Angella Charnot-Katsikas 34:14
You are now on unmute again.
So we see the slides, but we don't hear you there we go.

Paul W. Ladenson 34:18
OK, if there is a Evelyn, if there is someone there who could take over the changes, I'll just request them.
Let me know when you're in the driver seat.

Dr. Angella Charnot-Katsikas 35:19
If need be, we can see the slides even not in slide show, but Evelyn if you can put them on slide show that would be great.
We'll go from current slide.

Dr. Angella Charnot-Katsikas 36:00
So if let's click slide, show up at the top, and we'll go from current slide.

Dr. Angella Charnot-Katsikas 36:31
Great.
Please go ahead.

Paul W. Ladenson 36:33

And if I could have the next slide, please.

This cartoon illustrates the need for the option of testing more than one saddle. Logically indeterminate thyroid nodule in planning surgery in the top row you see examples of thyroid glands with a nodule in each lobe in the left hand top figure. Both nodules side electrically and determinant, but by molecular testing both benign, requiring only observation in the two middle panels of the top row, you see the different operations right and left lobectomies respectively that would be performed if only one of the nodules was cytologically indeterminate but suspicious by molecular testing.

And of course, in the right hand cartoon of the total thyroidectomy that would be performed if both nodules were genomically suspicious.

In the bottom row you see the analogous of need of for different operations. Should detection of the unusual thyroid malignancy medullary thyroid cancer be detected in either thyroid nodule of a condition for which bilateral thyroidectomy and central neck dissection is typically recommended?

Next slide.

The second, uh request that I'm making today is that we be enabled to use the prognostic value of molecular testing in patients who have Bethesda 5 suspicious for malignancy thyroid nodules among the genetic alterations revealed by such testing is the B raft mutation and I show you here 2 studies from our institution in which the recurrence rate and the mortality for papillary thyroid cancers has been shown to be greater among papillary thyroid cancers that harbor the be Raff activating mutation. Umm, the discovery of this mutation predicting a more aggressive malignancy preoperatively would typically lead to a recommendation for bilateral thyroid surgery in anticipation for the probable need for the patient to receive postoperative radioiodine therapy.

Next slide.

This is a study from two years ago looking at how molecular testing among patients with thyroid nodules that were classified as either suspicious for or diagnostic of malignancy.

How preoperative knowledge of that affected decision making about the extent of thyroid surgery and you can see in these two studies in blue and orange and then in grade the combined results that among patients in the right hand triple set where

there was no preoperative testing what in retrospect was the sub?
Thyroid surgical choice?
Uh.
In only approximately 2/3 of cases was the correct choice made, and in contrast, how preoperative molecular testing enabled selection of the optimal third surgical extent in more than 90% of patients.
Next slide.
No, this request and if you could just advance the slide with an additional click here to highlight how in the uh, updated Bethesda if you could go back and or I can simply point out if you'd reverse this.
If you look at the published last month revision of the Bethesda system for reporting thyroid cytopathology and the recommended clinical management for these categories at the second from the bottom row in this table, suspicious for malignancy, you can see that these revised guidelines in fact recommends molecular testing as an appropriate measure to provide the sort of prognostic information that I've just described and to facilitate the optimal extent of surgery as demonstrated in the last study and my final slide please.
So in conclusion, today I'm really making two requests, the 1st for a clarification of the need for potential molecular testing in more than one direct nodule among patients with multinodular glands, and secondly, to ask for consideration of the value of prognostic information from preoperative molecular testing in Bethesda 5.
Suspicious for malignancy.
Nodules.
And we're very hopeful that this panel will consider these issues and finalize a policy helping patients as soon as feasible.
Thank you.

C **Dr. Angella Charnot-Katsikas** 43:42
Thank you for your presentation.
Our next speaker is Doctor Paul Pagano, who will be speaking on molecular biomarkers for risk stratification of indeterminate pulmonary nodules following bronchoscopy.

PP **Dr. Paul Pagano** 44:07

Right.
Are you able to see my slides?

Dr. Angella Charnot-Katsikas 44:10
Yes, we can see them.
They're not in slideshow.

Dr. Paul Pagano 44:25
I seem to be having trouble with slideshow.

Dr. Paul Pagano 44:26
Let me see if I can make it a little bigger at least.
OK, first I would like to thank you all for the opportunity to speak about the proposed LCD and provide these comments.

Dr. Paul Pagano 44:39
My name is Paul Pagano.
I'm the CEO of Longlife AI by way of introduction, I'll be doing lung Cancer Research for the past 15 years.
1st at UCLA, where I studied the early events of malignant transformation and early metastatic behavior in lung pre malignancy.
And now here at my position at lung life here at long life, we are a diagnostics company focused on the early detection of lung cancer.
And we've developed the lung LB test.
This is a four color DNA fish assay using blood to aid in the evaluation of indeterminate lung nodules.

Dr. Paul Pagano 45:11
We believe that the lung LB test will provide important information to physicians that will enable avoidance of unnecessary procedures for individuals with benign lesions and reduce delays in treatment for those with malignant lesions.
In this presentation, I'd like to introduce you to long life and the test that we've developed, express our support for the proposed LCD DL3965 four and offer our comments for your consideration, which generally we feel will strengthen the proposed LCD by making it less test specific, which we believe to be in alignment

with mold's long standing approach of establishing foundational LCD's that enable coverage of categories of molecular tests for a particular indication to undergo the streamlined technical assessment process.
This is important because as MolDX is where multiple tests are in development that use analytes other than RNA and sample types other than bronchial epithelial cells obtained during bronchoscopy.
This includes our own test lung LB, which employs DNA fish on rare cells and blood, as well as various sites, perception, nasal swab test which utilizes RNA isolated from the nasal epithelium and just so you know, we do plan on submitting a comment letter, which we'll go through these points that we discuss in more detail.
As mentioned before, the Long Lab test is a molecular diagnostic assay that provides information and physicians considering the best pathway for nodule workout.
It utilizes what are called circulating genetically abnormal cells or CGCS, isolated from the whole blood and their identified using a four color DNA fish asset and an algorithm that we've developed that using machine learning detects these cells in a background of normal peripheral blood mononuclear cells.

PP **Dr. Paul Pagano** 47:04
These are then reviewed by a licensed technician prior to sign off by a pathologist and the test itself is reported as the individual either having an increased or decreased risk of having a malignant process.
The test has undergone analytic and clinical validity testing within our CLIA certified Kappa accredited laboratory in Thousand Oaks and Justice.
In 2022, we received approval from the New York State Department of Health for the Lung LB test.
Data from clinical validation study, which again was published earlier this year, suggests that the lung OB test performs equally well across different lung cancer subtypes and patient smoking histories, and a cohort that was largely comprised of individuals with intermediate risk modules.
These represent the most diagnostically challenging nodules to evaluate.
We also demonstrated well balanced sensitivity and specificity for the test, which suggest the potential of long LB to be used as both a rule in and rule out test and we're currently exploring that and an expanded validation study that is ongoing.
As stated previously, lung life supports the finalization of DL3965 four because molecular diagnostic testing for people with indeterminate lung nodules

demonstrates clinical utility and guiding the appropriate care for patients by Reese, stratifying the risk for malignancy delays and lung cancer diagnosis and subsequent treatment result in potentially significant reductions in survival.
This was demonstrated by a partners at Mount Sinai doctors Yankovitz and Henschke earlier this year as part of the early lung Cancer Action program.
Conversely, the process of nodule evaluation can lead to unnecessary harms in patients with benign lesions.
It's been estimated that up to 40% of all lung nodule biopsies are for benign inflammatory diseases and that in the community setting, 35% of surgeries for indeterminate lung nodules are on benign disease.
So clearly there's a need for both rule in and rule out style tests.
We believe the wheel be test will be capable of helping physicians evaluate indeterminate lung nodules and that our test meets the coverage criteria for DL3965 four and we look forward to engaging with Medicare and MolDX excuse me on the technical assessment process once the proposed LCD is finalized.
There are a few revisions that we would like to propose today and again generally serve to make the proposed LCD less test specific and more in line with MolDX's approach of a foundational LCD.

Dr. Paul Pagano 49:48
The first is not to limited by type of biopsy, because while bronchoscopy can produce indeterminate results, so can other biopsy types.
For example, transthoracic needle aspirate can produce a diagnostic specimen between 60 and 80% of the time.
This is largely dependent on nodule size, it's location and physician experience.
Additionally, there are individuals who are ineligible for biopsy due to health reasons or location of the nodule, particularly if it's inaccessible to biopsy and physicians are increasingly faced with having to manage these nodules when biopsies are not safe or feasible.
And so molecular testing should also be available in these cases, and generally this aligns with Doctor Billatos had mentioned earlier in the call that molecular testing would also be helpful to physicians if it came upstream of an invasive procedure like bronchoscopy or transthoracic biopsy.
So we suggest not limiting coverage of molecular testing to individuals.
Also, with no cancer history, there are certain cancer types that are not definitively

known to increase risk of malignancy when an individual has a lung nodule.
And importantly, we believe that narrowing of the coverage exclusion for prior cancer will not undercut MolDX's ability to evaluate these tests on an individual basis through the molecular.
Excuse me, the technical assessment process.
We also proposed not to limit coverage to intermediate risk modules.
As stated before, Tanner at all described higher rates of surgery on benign nodules and this is likely due to lack of pathological diagnosis in patients that were already at high risk for malignancy.
Additionally, assignment of pretest resembling Nancy varies by institution and physician, with some using risk calculators such as the Mayo nodule calculator.
Others physicians using their judgment or intuition, in other words, the determination that a patient is at high risk for a pulmonary malignancy should not eliminate or undercut the ordering physicians discretion to order molecular biomarker test for an indeterminate pulmonary nodule.
If they consider such testing to be medically necessary, once again, any rules governing the coverage based on patient risk level can be made on a test by test basis during the technical assessment process.
And lastly, Longlife believes that the coverage criteria that the beneficiary has not been tested with the same or similar assay for the same clinical indication should not apply an instances of a new nodule of concern or we're existing nodule has a change in appearance such that the risk of malignancy has changed.
Test developers should have the opportunity to prove test validity for these clinical scenarios by which proving longitudinal patient monitoring and this can be done again through the technical assessment process.
And I'd like to note that in CMS national coverage determination 92, the agency required that a patient not had been previously tested with the same test using NGS for the same cancer genetic content.
So you can think of this as testing of a new lung nodule or an existing lung nodule with significant change in appearance and be considered akin to testing for new cancer genetic content.
To briefly summarize, long life does support the finalization of this proposed LCD DL 39654 to establish coverage for molecular testing of indeterminate lung nodules.
We believe it allows for our lung lab test and others in the pipeline to be reviewed through the technical assessment process and that the recommended modifications

aligned well with mold's approach for creating a foundational LCD again to cover categories of molecular test.
Again, I'd like to thank you all for your time and attention.

Dr. Angella Charnot-Katsikas 53:45
Thank you for your presentation.
Ohh right.
And we are ready to begin our final presentation of the afternoon.
Doctor John Leite will be presenting on multiple policies, so I will turn it over to you.

John Leite, Ph.D. 54:08
Thank you.
Right.
Hopefully you can all see my screen.

Dr. Angella Charnot-Katsikas 54:16
Yes.

Dr. John Leite 54:18
Well, thank you and uh, on behalf of our side, I'd like to thank the MolDX medical director team and the staff were drafting these important LCD.
I'm here with other members of the varsity team to voice strong support and to provide comments and suggestions like to thank you for taking the time for this call and for allowing us the opportunity to comment.
Specifically, we like to express strong support for the two proposed LCD's that detail coverage for risk stratification of pulmonary and thyroid nodules.
And the third proposed LCD detail and coverage for testing to guide patient management decisions and castration resistant and metastatic prostate cancer.
Variscite recommends a specific edit to the draft DL 39654, whereby we suggest removal of the bronchoscopy requirement to allow for coverage of testing to be used prior to biopsy, and also clarify coverage criteria for perceptive GSC.
In current practice, further, we'd like to propose some further revisions to LCD's DL 39646 and DL 39636.
Parasites strongly supports the creation of a foundational LCD for a category of molecular biomarker tests that aim to risk stratify indeterminate pulmonary nodules.

We agree with the evidence cited that perceptive GSC is capable to effectively reassign patients from pretest intermediate risk to post-test low risk as well as patients from pretest low risk to pretest, very low risk.
With the aim to future proof, this foundational LCD and in light of technical and test development coming from parasite as well as other industry participants, some of which you've heard here today, we request that the requirement for bronchoscopy procedure be removed for the following reasons.
Number one, bronchoscopy could prevent or the requirement could prevent DLL 39654 from establishing coverage criteria for new and future tests that would otherwise meet the analytical validity, clinical validity, performance requirements. And yet may not require an invasive procedure to secure specimens needed for testing #2 perception nasal swab, which is currently being developed by PERICYTE, already demonstrates a high negative predictive value at 98% and positive predictive value at 70% using RNA expression from epithelial cells that are collected by a noninvasive nasal swab procedure.
And it's performed prior to or in lieu of bronchoscopy or other biopsy procedures. Data from this test has already been presented at multiple conferences, most recently at the 2023 American Thoracic Society Conference, and is now the subject of a manuscript that's pending publication #3.
There are multiple emerging applications that use blood based biomarkers at various levels of evidence.
One of these is already covered by CMS, albeit as a protein biomarker test and the number four.
We believe that a tech assessment is the opportunity for multidex to review such incoming applications for coverage consideration and to determine if the analytical and clinical performance of the proposed assays meet the threshold for coverage set by the LCD.
We furthermore proposed removal of the pretest risk as a criteria for coverage and with regards to coverage criteria 2C through D, we request removal of the criteria. That test is not recovered if a patient is assigned to an overall low or high risk for pulmonary malignancy, citing that testing of patients in these pretest risk categories may not alter the management of patients or significantly improve their outcomes as multidex correctly stated, these risk calculators performances often variable in routine practice and should be interpreted with caution.
We recommend instead.

Them all.
The excuse detect assessment process to determine if the test analytical and clinical performance meet the threshold for coverage in the proposed they'll see the for the populations used in the test study, future the tests may assign patients to risk categories more accurately, and we're concerned that in the absence of clarification or removal of criteria to three through D2C through D may limit coverage of such tests.
Further, we see clarification that the coverage criteria in 2C through D should not alter the existing coverage perceptive GSC under the LCD 36854 perceptive GSE is currently covered uh for low pretest risk.
Under the current perceptive LCD and the absence of our prior recommendation to remove pretest risk as a criteria for coverage, we ask for clarification that perceptive GSC coverage into low pretest risk indication should remain the same.
There's also the potential for misinterpretation that an ebus or an FNA must be performed prior to coverage of perceptive GSC, and our written comments will reflect these comments above and suggest some alternatives.
Switching gears now to DL 39646 in relation to assessment of thyroid nodule risk stratification, variscite would like to express strong support for the proposed draft LCD.
We agree with the inclusion of Bethesda 5 thyroid nodules as candidates for molecular testing, as this would bring Medicare coverage in alignment with the latest guidelines under the 2023.
But that's the system for reporting thyroid side of pathology.
Uh Variscite has one recommendation for clarification surrounding secondary nodule testing.
Our understanding is that implementation of the building article post issuance of the final draft will continue to allow for payment on appeal with support documentation in instances where a patient has a second unrelated nodule, or a patient has more than one indeterminant nodule.
Uh, now switching gears to prostate cancer.
Uh, very site would like to express its strong support for finalization of the draft LCD DL 39636.
We propose clarification to ensure coverage for new lesions.
The proposed LCD criterion 3 seeks to avoid repeat testing or testing with a similar test during the same episode of Care.

However, our written comments will seek to avoid inadvertently non-coverage of newly identified lesions during the course of a patient's clinical progression.
So with that, that is my final slide again, just want to reiterate our support for these LCD and we look forward to prevent providing more detailed recommendations during the written comments section.
Thank you so much.

C **Dr. Angella Charnot-Katsikas** 1:01:32
Thank you for your presentation and we thank all of our speakers this afternoon.
With that, we are going to go ahead and conclude this open meeting.
So thank you all and have a great rest of your day.

JP **John Leite, Ph.D.** 1:01:51
Thank you.