June 28, 2021 Jurisdiction M (JM) Open Meeting Transcript

Dr. Judy Volkar:

I have just started the recording of this open meeting in compliance with CMS. For the record 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. I will now introduce the speakers one at a time. I would like to remind the speakers to please keep your presentation to 15 minutes at most so that all the speakers may present. If you start to go over, I actually have a timer that will go off with a little sound reminding us the need to conclude. Dr. Paul Gerrard is our first presenter, speaking on MolDX: Biomarkers to Risk Stratify Patients at Increased Risk for Prostate Cancer on behalf of DH Diagnostics, and Beckman Coulter. Dr. Gerrard? Whoever is speaking unless you are presenting, please put your phone on mute.

Dr. Paul Gerrard:

I sent a PowerPoint presentation ahead of time and I will refer to all the page numbers on that. It has no graphics so even if it's not right in front of you, most of what my verbal comments are will capture the text on the PowerPoint. As noted, I'll be speaking with regard to MolDX: Biomarkers to Risk Stratify Patients at Increased Risk for Prostate Cancer on behalf of DH Diagnostics and Beckman Coulter. And I'll go to slide two.

A key question we have is what is the scope of this LCD? The LCD is a MolDX LCD. However, the language of the LCD does not state that it's limited to molecular tests. The draft LCD right now says that the LCD will provide quote unquote, "Limited coverage for prostate biomarker diagnostic tests that help differentiate men who may or may not benefit from a prostate biopsy when all the following conditions are met." End quote. So it is not limited to molecular tests, even with a MolDX policy.

We will also add that the review of the evidence includes non-molecular tests, for example, the prostate health index or phi, which I will speak a little bit more about in a moment. In spite of that, MolDX has consistently stated that its scope is limited to tests of human DNA and or RNA. And then the coverage article only mentions molecular tests. So with this set of facts, we were trying to understand what the scope of the LCD is, whether it is really limited molecular tests, or whether it is a MolDX LCD that applies to non molecular tests as well.

And so, I'll go to slide three. This is really the key question, are non-molecular tests within the scope of the LCD? If the answer to that is no, then we ask that MolDX clearly state in the LCD and the article that the policy only applies to tests of DNA and RNA. And we also ask that MolDX make it explicit that non molecular tests not addressed by this LCD may still be covered. In that case, they would be subject to either other local coverage determinations or on a claim by claim basis.

With non molecular tests are within the scope of the LCD and this is intentional, then we recommend that MolDX add language covering PHI in the associated billing and coding article along with the appropriate CPT codes. Additionally, if the test will require a Z code, we ask that MolDX in the collaborating max make an effort to educate providers well in advance of the Z code requirement being effective, to give them time to modify the revenue cycle processes.

Since PHI is not a molecular test, it may be run by many labs that have not been subject to Z codes in the past, and they will need to not only register this test, but they will need to register their lab and transform the revenue cycle processes to accommodate what is essentially a new requirement to them, even if they've been located in a jurisdiction that has the Zika requirement. We've also asked that MolDX update its manuals and provide education to the provider community about its new expanded scope, in this case to non-molecular tests.

I'll go on to slide four here. PHI is not a molecular test. We just want to make that clear and it's not an algorithmic test. It uses an immunoassay to measure three annulments which are PSA, three PSA, and P2 PSA. It can be run by any lab that is able to measure the analysis, including community labs that do not perform molecular diagnostic tests. And PHI calculated using the Beckman Coulter hypertech assays is indicated for use as an aid in distinguishing prostate cancer from benign prostate conditions, and for prostate cancer detection men aged 50 and older with total PSA in the range of four to 10, and with digital rectal exam findings that are not suspicious for cancer.

So, this is generally in line with the coverage criteria of the LCD in terms of what's on the FDA label for this test. The evidence that exists in support a PHI, let we emphasize, we don't think five should be part of a MolDX LCD. However, if the LCD is intended to include non molecular tests, we believe that the evidence summary MolDX provided in the LCD, articulates that Phi meets a coverage criteria of the draft LCD.

Quoting MolDX own evidence review, the prostate health index PHI is a blood based immunoassay that uses PSA, 3PSA and P2 PSA to calculate a score that categorizes a patient's risk as low, moderate, or high. Studies have shown that the PHI significantly improves the sensitivity of prostate cancer detection, reliably discriminates high grade cancer, and can significantly reduce the rate of prostate biopsies. It sounds from that evidence review that MolDX has in fact reviewed evidence that would suggest that the test should be covered.

We genuinely support coverage of prostate cancer test to assist with a biopsy decision. But we believe that it's inappropriate to subject PHI to the coverage restrictions placed on molecular tests since PHI uses an immunoassay technology that can be used in community health centers for patients that have challenges with access to specialty care. We also ask the LCD to be modified to permit the use of PHI in primary care settings if PHI will be subject to this LCD.

Finally, as I noted previously, we asked that MolDX update the article to be consistent with the LCD with the following CPT codes for PHI to be added to the covered codes in the billing and coding article, which are 84153, 84154 and 86316. And with that, I will stop and take any questions.

Dr. Judy Volkar:

All right. Well, thank you Dr. Gerrard. And now our next presenter is Dr. John Vetto, speaking about MolDX: Melanoma Risk Stratification Molecular Testing on behalf of Oregon Health and Science University.

Dr. John Vetto:

So I will be using my slides and I will be showing graphics. So, if the staff wanted to go ahead to my first slide. I assume you have it in front of you. Great. So this is a slide that says clinical use of 31-GEP in melanoma review of the evidence. I am John Vetto, I'm a surgical oncologist at the Oregon Health and Science University in Portland. I run the high risk multidisciplinary melanoma program here, it's a large program with a huge catchment area in the Pacific Northwest patients traveling hundreds of miles. And that'll be a theme today, particularly for our Medicare age patients and using the tests to stratify and guide their care and simplify their care.

I do have to disclose that I work with Castle Biosciences that makes the 31-GEP. I will also say, however, that I'm not being compensated to speak today, that I'm appearing as an interested clinician who uses this test and believes in it. I'll also say that I'm going to present papers that I published that show independent analysis of the data, particularly the Arnott paper, Sam Arnott was a fellow in our lab, and he is the first author, I'm the senior author on that paper, and that paper was an independent analysis and received no support.

Okay, next slide. That's a little background on OHSU and our use of the tests with several members of my division and the Department of Dermatology have studied the test here and published on it. So we have good experience with it. I'll be dividing my comments today into two categories. First of all, showing how the test informs a subset of patients. Very low risk for sentinel node biopsy can guide the decision to do or not do the biopsy, particularly in the Medicare age patient. And secondly, I'll be showing how regardless of sentinel node status, how the test can help us adhere to guide surveillance in patients. And as you know, current NCCN guidelines are all across the board on that and somewhat chaotic, and I think the test brings order to chaos for the follow up of melanoma patients. Therefore, in my paper that I co-authored with Sam Arnott, we made this statement 31-GEP as prognostic information to the evaluation of primary cutaneous melanoma and should be considered in patients referred to sentinel node biopsy, which is the breadth of patient I see.

I want to stress next slide that we are an NCI designated cancer center, we have this large multidisciplinary program. And one of the themes I'll be using today is that the GEP improves our ability to assess patients. It does not replace staging. We use it in concert with staging and I'll show you that today. The Grossman and Marchetti particles were fairly limited in their scope because they weren't written by Commission's who do the breadth of what I do, in fact I find it somewhat ironic that the Marchetti paper concluded that the tool was useful for low risk days to patients and for high risk stage one patients is exactly what I'll be showing.

They had that finding, but they didn't know what to do with it. Because I think it's important for Palmetto to hear from clinicians like myself, who have considered the data and are integrating it into actual clinical practice, particularly with a focus on Medicare age patients. So again, I'll divide the talk into these two parts, the first part is how to optimize sentinel node biopsy choices. So on the next slide, I'm on the side with the blue graph, the graph says stays on the left and femoral node positivity risk on the right.

The right side is the NCCN guidelines, are the NCCN guidelines for single node biopsy? And for the non surgeons in the crowd, the NCCN tells us to do single node biopsy if the risk of a positive sentinel node is greater than 10%, and not to do it if it's less than 5%. And to consider and discuss it if it's in between.

However, the NCCN doesn't tell you how to do that, how to know the percentage risk of a positive sentinel node . On the left side of the Society of surgical oncology guidelines but they're made up, they're just correlated histopathology with risk, which is not enough.

And if you do that, as all my colleagues across the country know, the risk of a positive sentinel node across the board in your database is 11%, which I think is very low. That means 89% of the time, the test it's reassuring, but it really isn't changing practice. So we want not to have 100% chance of a positive sentinel node , but we want to enrich sentinel node . Not necessarily do it less, but do it smarter, particularly in older patients where they're co-morbidities and going to the operating room is not a small consideration.

Next slide is a graph with blue, black, and red colored dots. This is a study that we did and published in future oncology on the first author. And what we did here is we correlated the 31-GEP score or class with the chance that the patient was sentinel node positive. So we looked at 1400 patients, we called out about 500 who are of Medicare age, and drilling down just in patients older than 65, you can see that if you had a lowest risk, which is class 1 A that's that blue triangle, your chance of having a positive sentinel node was way below the NCCN cutoff of 5%.

On the other hand, there is patients who are in fact, their risk is higher than 10% because they have a class 2B which is the highest risk result. So what we would do is advise the patients in the blue group to not have sentinel node biopsy and in the red group to consider it. And if they have comorbidities that prevent them going to the operating room, this is the patients will follow per MSLT2 guidelines, which is ultrasound of the nodal bed and examine the nodal bed every four to six months for a couple of years. So called watchful waiting.

In the study when we model this, we said, "Okay, we want to do." If we didn't do sentinel node in those Medicare patients who had sentinel node because this was actual data. If we had done that, we would have enriched the positive sentinel node rate in the entire study from 11% to 22%. And I imagine if we limited that just to Medicare it would be higher. So we're doing sentinel node smarter.

We have made this change at Oregon, what we've done is patients present to us with stage T1 or T2, that's the vast majority of patients who come to us as thinner melanomas for sentinel node staging. If they're class 1A and Medicare age, we have them sign a consent that says, "I understand my data. I'm electing not to have it." That's done on a registry study so that it's all transparent and prospective. And then we do low intensity management because the risk of a channel note is so low.

I will say that since my study was published, we now have substage data to drill down and to get very granular into the patient's sickness and it continues to bear this out. On the other hand, if they have an intermediate score or particularly a high risk score, then we discuss enough of the sentinel node, either do it or again, if their comorbidity is prevented, then we follow them with watchful waiting.

Next slide. This is another title slide. So going on to the second part of the talk, the second utility of the 31-GEP is informing follow up decisions. And again, this is all across the board in the NCCN guidelines so we want to bring order to chaos and say, who are the patients who need more follow up and who are

the patients who don't? So, this is a meta-analysis I ran in the Sam Arnott study, I looked at VP class sentinel node status, and the combinations thereof. And again that theme of using both.

What we found is if you go to the bullets are in all patients at any stages, class one A and class two B were associated with significantly different risks. A positive sentinel node, I showed that in the previous slide. Secondly, patients with a low risk or at a three full lower risk of recurrence even compared to negative sentinel node patients. And finally patients with a negative sentinel node biopsy who are thought to be low risk by JCC but had a high risk GEP score were eight times more likely to fail to occur than the 1A patients.

Next slide. And to look at this visually, this is the blue bar graph on the next slide. On the far left are the so called double negative patients. These are patients who have a low risk for a distant failure because they're a class 1A GEP, and a low is for a nodal failure. And again, this is the non health study and paradigm of thinking is looking at patients holistically, where will they fail? So patients can have a nodal metastatic phenotype that's measured by sentinel node, or they can have a distant metastatic phenotype better measured by their GEP score. We want to know both.

So, on the far left are patients who have neither phenotype. These are the patients who can go back to their dermatologists only they don't need to stay in the high risk clinic, they don't need to drive there. That's particularly useful in the Medicare population. On the far right, are the double positive patients. Those are patients who have both a high risk for nodal failure and a high risk for distant failure. We need to keep those in the high risk clinic. And the interesting patients are in the middle. On the second bar are patients who are low risk but sentinel node positive.

Those may be the patients that we actually cure with sentinel node and don't need a lot of follow up, don't need a lot of immunotherapy, a great question for future studies. The third bar the patients where they are high risk even though the HAC says they are low risk, because they're sentinel node negative, those are the patients that we do not want to send back to dermatology only we keep those in the high risk clinic. We do surveillance, how do we do surveillance? Per NCCN guidelines with cross sectional imaging every six months. And here's another way of showing how the tests are used together.

These are the survival curves of the patient with a negative sentinel node biopsy as we all know, they continue to decay because patients with a negative sentinel node may have a distant metastatic phenotype and are dying of distant disease. So what do we do? We run the test and next slide, you'll see the animation, we run the test and the blue if you focus on the DMFS, the distant metastasis free survival, the blue bar are the double negatives, the red bar are patients who are sentinel node negative, don't have a nodal metastatic phenotype, but are higher risk of distant metastatic distant failure.

Not a death rate, not a death sentence as was pointed out by the Grossman paper. But still these are the patients that we can shift resources to. So we're shifting resources from the blue line to the red line. And remember, there's a lot more blue line patients than there are red line patients, we've done a cost analysis here at Oregon, it's a wash, we're not spending more money, we're just spending our surveillance dollars smarter.

Here's from our meta-analysis and some points from this meta-analysis from the Arnott paper that I published. GEP independently predicted relapse in the low risk patients. I'll show you that on the next slide. A GEP class two resulted in a significant independent predictor of recurrence and distant metastases in addition to stage, and a 31 GEP should be used in conjunction with stage conjunction with sentinel node if it's appropriate to do the sentinel node. So we use them together. That was not understood in the Grossman paper because of the dermatology group. They're not looking at the overall patient picture.

And just to drill down into that first bullet on the next slide. This is a paper we wrote with Brian Gasma at the Cleveland Clinic, myself and Dr. Leachman. And here we show that this is a study of just we looked at the first 690 patients who'd had the study, we called out 400 who are AJCC low risk, again, sentinel node negative or not appropriate for sentinel node . And then we ran the test. And there's those double negatives in the blue, and there are the patients on the red line who yes, they're low risk by AJCC, but a higher risk of failing. Statistically significant shifting resources at Oregon from the blue line to the red line, using our resources smarter.

Next line. And again, to summarize what we're doing so far, this is what we're doing at Oregon. Patients come in, they have sentinel node if it's appropriate, we're guiding the sentinel node biopsy with the GEP test, once it's either done or felt not to be needed and they're deemed low risk. If they're low risk and low GEP score they're that top blue line, those are the double negatives. They have low intensity management, they don't need to stay in a high risk clinic. We don't need to spend resources on them.

The second red bar, the second bar are the flip side patients who are low risk by JCC but high risk. Again, we're increasing intensity, shifting resources from that first blue bar to that second red bar. At the very bottom is that red bar, those are the double positive patients, they stay in the high risk clinic, we put them on clinical trials. We watch them very closely. Everybody does that. The interesting question for the future is what about that middle blue bar? Those are patients who yes, they're higher risk stage by AJCC because they might have a positive sentinel node, but they are low risk for failing distantly. Can we really decrease intensity? Great study question in the future.

We are writing at Southwest Oncology Group collaboratively proud for the second group, the red bar, which is patients who are high risk by the GEP score but deemed a low risk. In this trial, we propose to randomize those patients to get or not get that high intensity follow up. Some of us have been doing that follow up, and we're currently calling our data for major university centers, calling our data to write a pilot study. And then we hope to propose this to the Southwest Oncology Group.

Next slide is actually my last slide if you ignore the last slide in your deck, which was just an extra slide but I'm now on a slide the final summary slide that says utility of 31-GEP. This is a summary slide, we're using it for four reasons. Number one to identify patients who are at risk of sentinel node metastases. That was the first part of my talk and enrich the sentinel node biopsy, particularly in Medicare age patients, where they most often have a low risk. Secondly, to identify those double negative patients who have a low JCC stage and a low genetic risk and to get them out of the high risk clinics. Thirdly, to identify low risk patients by JCC who are actually high risk patients for distant failure. And to shift resources from that second bullet to that third bullet. I did not have time to talk about the 3A patients.

3A patients, as you may know, are patients who are stage three only because they have a micro metastasis in their node.

Famously they do well, but for they were left out of the FDA's analysis of the data, they're left out of the prospective randomized trial for the newer systemic therapies. But the FDA approved those treatments for all stage three. So the question is, can we use the test to stratify 3A patients into the high risk 3As and a low risk 3A? So we're treating those patients with science instead of geographic bias, which is what a lot of medical oncologists are currently doing.

We're using the data from a GP at Oregon to look at 3A patients and try to determine if they're high risk or low risk. Another great prospective trial for the future. I recommend to Palmetto that the LCD includes the recent papers, my paper, Sam Arnott's paper. It was published in the American Journal of surgery a few months ago. And again, that's the Oregon experience. Again, it's independent, there was no support for that paper, that's our experience. And the Netty Shay paper which has not been a very experienced at Wash U and St. Louis, published in JCL precision oncology. Now with that, I'll stop and ask if there are any questions.

Dr. Judy Volkar:

Thank you, Dr. Vetto. Our next presenter will be Dr. Matthew Goldberg, who is also speaking about MolDX: Melanoma Risk Stratification Molecular Testing on behalf of Castle Biosciences, Incorporated.

Dr. Matthew Goldberg:

Thank you very much. I want to thank all my medical directors for the opportunity to just come up today on MolDX: Melanoma Risk Stratification Molecular Testing here. So my name is Matthew Goldberg. I'm a board certified dermatologist and dermatopathologist and medical director at Castle Biosciences. For conflict of interest, I'm an employee and stockholder of Castle Biosciences. And for the presentation, I'll call out the slide and page numbers on the submitted PDF to help everyone follow along with the presentation.

So, on slide number two, my comments today I'll review the evidence that supports the existing LCD, Highlight new publications that have been published since the LCD went into effect, includes the suggestions for changes to the draft LCD that is currently open for comment. The existing LCD L37725 is based on a strong body of evidence that has only been strengthened since the last reconsideration. Okay, so I'll continue here on slide number three if that's okay.

The existing LCD here on slide three was approved by all formats and based on 22 peer reviewed studies, which demonstrate the consistent ability for DecisionDx-Melanoma gene expression profile or GEP testing to improve the accuracy of defining risk of health outcomes for health outcomes of interest for patients who have received this test result. There's also a clear clinical utility to identify patients who can safely forego the set molecular biopsy procedure and define risk appropriate patient management plans independent from decisions to consider the sentinel lymph node biopsy procedure itself.

Moving on to slide four, the next five slides were previously presented at an open meeting in October 2019. And DecisionDx-Melanoma was developed and validated to assess risk of recurrence and

metastasis independent from traditional clinical pathologic factors for patients with stage one through three melanoma. In the test risk stratify patients with a class one and class two result with the lowest risk in the class 1A group and the highest risk in the class 2B group.

The full term on the next slide five highlights how DecisionDx-Melanoma helps physicians answer two questions that inform important clinical decisions and influence patient treatment plans. Specifically what is the risk of a positive sentinel lymph node to inform sentinel lymph node biopsy recommendations? And secondly, what is the patient's risk of recurrence and metastasis after a melanoma diagnosis to inform decisions such as appropriate level of follow up imaging and multidisciplinary referrals?

In the pink and white figure on the next slide number six, AGCC version eight staging provides risk stratification for patients diagnosed with melanoma and DecisionDx-Melanoma improves the prognostic accuracy of this risk stratification across stage one through three melanoma, demonstrating how AJCC provides a population based risk for each stage which can be further stratified by combining the independent prognostic information from the GEP result.

For example, AJCC version eight predicts that a patient with stage two disease has a 90% five year melanoma specific survival or MSS. Seen here with a black dot in the central column. However, as the up and down arrows indicate the same patient would be predicted to have a five year melanoma specific survival of greater than 99% with a class 1A GEP result, which compares to an almost 84% five year MSS with a class 2B GEP result.

On the next slide number seven, for sentinel lymph node biopsy guidance DecisionDx-Melanoma identifies patients who are at low risk of sentinel lymph positivity who can safely avoid the procedure based on the currently accepted risk threshold of 5% predicted positivity. In the Medicare population DecisionDx-Melanoma identifies a subset of patients with T1 and T2 melanomas, meaning invasive melanomas that have a two millimeter breastbone thickness or less who fall below this 5% predicted risk of sentinel lymph node positivity.

And here in this table from data and large cohorts, those patients with a class 1A result have a 1.6% rate of sentinel lymph node positivity and avoiding sentinel lymph node biopsy in these patients can reduce unnecessary surgical procedures, while allowing improved resource allocation to those patients with elevated risk for positive sentinel lymph. In the next summary slide on slide eight is information presented previously and reinforced by Dr. Vetto's presentation just now, DecisionDx-Melanoma influences sentinel lymph node biopsy discussions and decisions for patients with invasive melanomas two millimeters in thickness or less.

And further DecisionDx-Melanoma influences decisions for follow up imaging and multidisciplinary referrals for patients with melanoma greater than or equal to 0.3 millimeters in Breslow thickness. You can move forward to two slides to slide number 10. The next three slides here focus substantially on how DecisionDx-Melanoma impacts the performance of sentinel lymph node biopsy decisions in the Medicare population with melanomas two millimeters in thickness or less.

Again, one of the main findings from that overall paper in 2019 is that patients in this group who receive a class 1A result actually have less than 5% predicted risk of sentinel lymph node positivity and can therefore safely forego the surgical procedure. In the figures on the right side of the slide take this finding a step further and highlight that if the class 1A patients are managed according to these findings. 65% of patients in this cohort could safely forego the sentinel lymph node procedure.

And this ability to reduce unnecessary sentinel lymph node biopsy procedures also holds for T1 and T2 melanomas when viewed separately as seen here on the bottom right of this page. It's important to re-stratify patients with thin invasive melanomas because Medicare eligible patients with T1 and T2 tumors currently undergo the sentinel lymph node biopsy procedure. And while guidelines may not endorse the sentinel lymph node biopsy procedure in patients with T1A melanoma, it remains important to triage these patients and significant numbers of Medicare eligible patients with T1A melanoma currently undergo a sentinel lymph node biopsy.

And what's more, approximately 42% of patients with T1A melanoma undergoing the sentinel lymph node biopsy procedure do not have high risk features. On the next slide number 11, there are stick figures and for illustration purposes, we've modeled what this looks like in current practice based on data from surgical oncology centers. In patients with T1A melanoma 65 years and older that have the sentinel lymph node biopsy procedure performed, 94% will have negative results and receive no benefit from the procedure and those are highlighted here in gray.

On the next slide number 12, in the patients who underwent a certain lymph node biopsy surgical procedure as part of their clinical care, DecisionDx-Melanoma identifies 82% of patients with a class 1A result who can safely forego the sentinel lymph node biopsy. And these figures are highlighted in blue. GEP testing in this group would reduce a large proportion of unnecessary procedures while improving the yield of sentinel lymph node positive results in surgical procedures still performed for non-class 1AT results highlighted in the gray and red.

Switching gears now on slide number 13, independent from SLNB decisions, clinicians treating patients with melanoma are also looking to address the question of what is the risk of recurrence and metastasis to their patients? Published evidence by Mark Sedal established a floor for GEP testing at 0.3 millimeters of Breslow thickness or greater. And the data support the 0.3 millimeter cut point for re-stratification of patients who may be elevated biological risk of recurrence and metastasis and whose clinicians will change management following GEP results.

Importantly, both clinical utility studies analyzed in the Mark's paper reported the proportion of management decision changes prior to publication to Vetto et al 2019 manuscript, that describes the use of the test to inform sentinel lymph node biopsy decisions as discussed in the prior slides. Therefore taking together the clinical utility of DecisionDx-Melanoma described in Marks et all combined with the ability to avoid unnecessary sentinel lymph node biopsy procedures described in Vetto et all 2019 highlight the significant clinical actionability of the test for patients with T1 and T2 molecules.

Slide 14, since the reconsideration request in 2019, evidence supporting the utility of DecisionDx-Melanoma has increased. The reconsideration of evidence included in the draft LCD you should include

the whole body of recent evidence, some of which are listed in the table here on the slide. Now moving to slide 15, the inclusion of supportive articles shown here in this table and a revision to the LCD is important because we provide an improved context and evidence available for the DecisionDx-Melanoma test.

Specifically, these additional articles below address points raised in the recent added text of the draft LCD. For example, all stage one and two patients included in the Greenhall meta-analysis have been staged using AJCC version eight staging, and the paper includes multivariable analysis that demonstrates the statistical independence of the DecisionDx-Melanoma test results from the clinical pathologic factors incorporated in staging. The same can be said for not in shay at all as well.

And for the next several slides, we'll walk through the highlights from Greenheart and Shay studies. First here on the table on slide number 16, DecisionDx-Melanoma is consistently a significant predictor of risk independent of all relevant prognostic clinical and pathological features across multiple studies. It's important to highlight that outside of the AJCC version eight staging there is no other nationally accepted tool available that integrates all clinical and pathological features to provide prognostic information.

Therefore, evaluation of the ability of DecisionDx-Melanoma to improve the accuracy of defining risk for tested patients has focused on comparisons to multiple chronic pathologic factors, and AJCC version eight staging. The table here on the next slide number 17 is adapted from the Greenheart at al meta-analysis and demonstrates that in a cohort of 1479 patients DecisionDx-Melanoma significantly stratifies risk within AJCC stages.

This study highlights how DecisionDx-Melanoma can serve as an adjunct to staging, not a replacement for staging. And survival rates for AJCC only demonstrates stratification melanoma or MSS cannot give specific information on recurrence free survival RFS and distant metastases survival DMFS. This information is used by clinicians to guide important management decisions such as frequency and follow up, imaging and referral to multidisciplinary clinics.

On the next page slide 18 table, the DecisionDx-Melanoma significantly stratifies risk within AJCC stages and provides added prognostic information to an approach that relies on staging alone. Based on the recent prospective study from Shay et al, patients with early stage disease and high risk class 2B results have a recurrence risk similar to patients with later stage disease are currently recommended to receive more intensive follow up and surveillance imaging and referral to multidisciplinary care. So in this way DecisionDx-Melanoma testing identifies a level of risk in early stage patients that is determined to be clinically actionable by national guidelines.

Further on slide 19 the next slide, the table adapted from Dr. Shay et al shows the overall sensitivity of risk prediction is enhanced when DecisionDx-Melanoma and AJCC version eight stage tumor combined. DecisionDx-Melanoma is more sensitive than AJCC version eight staging alone for prediction of RFS, DMFS and death. And when combined DecisionDx-Melanoma and AJCC staging accurately identify 76% of recurrences metastases compared to 57% of recurrences and 62% of metastases if AJCC is used alone.

Again, this recently published prospective multicenter study should be considered by the draft LCD as it demonstrates the DecisionDx-Melanoma, improves the accuracy of defining risk for health outcomes of interest for tested patients. On the next slide number 20 in the table adapted from Greenheart et al in a cohort of 867 patients with both GEP testing and sentinel lymph node biopsy performed, which showed the DecisionDx-Melanoma outperforms the prognostic accuracy of sentinel lymph node biopsy for the endpoints of recurrent and distant metastasis.

It is more in the bottom rows either a positive sentinel lymph node biopsy, or request GEP result. The accuracy metrics for risk prediction improved further and achieve a sensitivity of 88% for RFS, and 90% for DMFS. This again highlights that DecisionDx-Melanoma augments current re-stratification approaches when GEP results are considered in the context of AJCC staging. Moving now to an overview perspective on slide 21. Since 2018, the original LCD effective date, DecisionDx-Melanoma has been ordered on Medicare age patients by 4700 clinicians at over 2700 institutions, including 40 leading academic centers.

DecisionDx-Melanoma has been included in the multi-disciplinary workflows in many academic hospitals to integrate AJCC staging, and DecisionDx-Melanoma testing across the spectrum of patients with stage one through three melanoma. In conclusion on slide 22, data published to date continue to support the validity and utility of DecisionDx-Melanoma to identify patients with tumors two millimeters in thickness or less, who have a low risk of metastasis to the sentinel lymph node surgical procedure.

We request consideration of research that evaluates DecisionDx-Melanoma test results in conjunction of AJCC staging and other clinical pathologic features to improve the accuracy of risk prediction for patients with stage one through three melanoma. Articles recently added to the draft LCDs are the only author's name specifically in the draft text of the LCD do not contribute additional tested patients to the published literature that have limitations that are not currently outlined in the draft LCD.

Endorsement articles and opinions statements informed by survey data with a low response rate of 14% to both surveys, and Marchetti et all does not make comparisons of the accuracy of GEP testing to the accuracy of AJCC staging alone, or consider the improvement in prognostic accuracy provided by combining gene expression profiling with AJCC staging approaches as has been performed in studies such as Greenheart et all, Shea et all or Naud et all and others. What is more, both articles do not address the clinical utility of the DecisionDx-Melanoma test to inform sentinel lymph node biopsy decision making.

Around 8000 clinicians in 1000s of institutions have also adopted the DecisionDx-Melanoma test to improve patient care and there are many physicians with clinical experience agree test results can be incorporated to inform management decisions. And finally here in the last slide number 23, where we will submit specific language for draft LCD modification during the open comment period, broadly speaking, we recommend removing the two paragraphs recently added to the draft LCD that site the Grossman and Marchetti articles.

And in the event that the two proposed paragraphs remain in the LCD, we recommend including a discussion of limitations of both articles, as well as a thorough discussion of the numerous studies

published since the LCD went into effect that further support the prognostic accuracy of DecisionDx-Melanoma, that guide sentinel lymph node biopsy decision making, and augment risk prediction for recurrence and metastasis, many of which were discussed in this presentation. Thank you for your time and attention.

Dr. Judy Volkar:

I would just ask everybody remind you please, to put your phones on mute if you are speaking and you're speaking in a place that there are other conversations going around to please ask the people around you to be quiet during your presentation because it's very distracting to hear those extra noises in there.

Dr. Gabe Bien-Willner:

Can I ask Dr. Goldberg a quick question on his presentation? This is Dr. Bien-Willner.

Dr. Matthew Goldberg:

Sure.

Dr. Gabe Bien-Willner:

Matthew, just a quick question. Is there any of the literature that you've presented here, does any of it enumerate or discuss explicitly that upon use of the test physicians are actually in demonstrably not getting sentinel lymph node biopsies? Let me clarify one step further, when the test is determined to be negative, that they subsequently follow the guidance of the service and preclude the need of a sentinel lymph node biopsy and subsequently do not perform that procedure?

Dr. Matthew Goldberg:

There are manuscripts published where centers are following this guidance. So for example, the Arnott et al study is based substantially in clinical practice where clinicians are using the GEP results to inform decision making. But I'm not sure that I understand the question specifically.

Dr. Gabe Bien-Willner:

Okay, let me explain a little further. The intended use of this test as per the initial draft manuscript is that utility of the test in understanding whether the patient is likely to have a positive sentinel lymph node biopsy? Under the existing policy the understanding is that if the patient has this test performed, and the test result demonstrates that the patient would not likely have a positive sentinel lymph node, then the patient does not require a sentinel lymph node biopsy. So the question is trying to understand beyond the accuracy of the staging information is the utility of the information, and really just a confirmation that in fact, when clinicians use this test, they actually make them determine the interventions of the patient based on its results.

Dr. Matthew Goldberg:

We have ongoing studies that are currently open in evaluating how clinicians incorporate take up the DecisionDx-Melanoma test result and altered their management for the guidance of sentinel lymph node biopsy procedures. And an ongoing clinical trial that continues to enroll patients called the decide to trial here. But I don't believe that in the articles that we've listed here to be added to the LCD that we

have data on patients tested and then whose specific pathways are modified with specific outcomes as a result of those modifications.

What we do have though are multiple prospective studies that demonstrate that patients who obtain a real risk class 1A result go on to sustain excellent five year health outcomes, specifically the Shae et all article from 2021 JCLPO paper demonstrates that low stage patients with a high risk result sustained worse outcomes than would be suspected. And in contrast, the high stage patients with a low risk class result sustained excellent five year health outcomes. But that paper, for example, does not track the management decisions specifically made based on the guidance of the test. That clinical trial is currently ongoing to demonstrate that result. Our clinical utility studies describe how clinicians use this data to modify the decision making. And those are also listed as separate clinical utility studies that describe how this information is used. And then again, just that Arnott study, Arnott study rather, is at a center where those decisions are being followed and implemented in the health outcomes are tracked there.

Dr. John Vetto:

This Dr. Vetto. Can I comment?

Dr. Gabe Bien-Willner:

Please do.

Dr. John Vetto:

Like Dr. Goldberg said we don't have any data on that published as of yet. I can tell you there are institutions like ours and Wash U and many others where this is being done. I can't give you any published quantified data. After the future oncology paper was published, we felt it was appropriate to design and roll out the decide study which is a prospective registry study where the patient signed a consent saying I had the discussion. The sentinel node was not done. I consent to that, because remember, we're doing less than the standard of care here for some patient. And maybe we're staying on it because as Matt said, we believe there's a lot of T1A patients who are having sentinel node who didn't need it anyway, but the test confirms that. So anyway, now we're getting with a side study open, we are now getting that data, you bet we'll publish that when we get it. I will say that because of COVID, that whole thing has been sort of slowed down. We just opened that study at Oregon, for example. And we're just starting to accrue our first patients. So yes the data is coming, but not published yet. We're just opening the design study on a broader group of centers now. Does that answer your question?

Dr. Darrell Rigel:

This is Dr. Rigel, I know I'm the next speaker, you'll see in my slides there are actually three clinical utility studies specifically that looked at if you had the results of the test, were you less likely to do a sentinel node biopsy for it? And it specifically showed that, all right. Three of those that are out there that are peer reviewed studies, all right. So, I save a lot of time.

Dr. John Vetto:

All right, very good. Thank you.

Dr. Judy Volkar:

So thank you, Dr. Goldberg. And then our next presenter is Dr. Darrell Rigel, who will be speaking on MolDX: Melanoma Risk Stratification Molecular Testing on behalf of the New York University Grossman School of Medicine.

Dr. Darrell Rigel:

Well, thank you very, much appreciate the time It's kind of tough, I'm not able to see the slides, but I know them and I could go on and I'm going to handle a lot of these things that we covered already by doctors Vetto and Goldberg. So what I'm going to try to do is just really give you a high level background for it. Just by way of my background, I am a melanoma researcher, I've done over 250 papers, over 1000 lectures in my life.

My claim to fame is that I helped evolve the A,B,C,Ds of melanoma, it's been over 40 years that we published that. It's an area that I'm particularly concerned about because I deal with patients and my practice is focused primarily on melanoma patients. If we got to slide two, again, there's a lot of new studies that are there and a variety of things. So I think there's two things you take away from what I'm telling you today. One is that the data strongly supports the value of this test and continuing the coverage of this test. And secondly, that it's really important to maintain the current policy as is because the fact is that this really is important for my patients, we use this on a regular basis, we could better assess prognosis. And we do use it in fact to recommend whether or not we could avoid and not do a sentinel node biopsy for that. If I could have the next slide please number three. Again, you can see there's a number of studies there at the top of the slide and why we want to continue this. But I'm going to talk specifically about the Marchetti study, and the Grossman study.

I know both these people, they're very nice people. But they've really misinterpreted the data in a variety of ways. I think what Matt said was very important that if you're going to include these papers in the LCD, you have to conclude the overwhelming majority of supporting papers, new supporting papers that are in there, because I think that makes a difference. If we could go let's talk about these articles a little bit, and I think just to preface it by saying the Marchetti study is really opinion, neither of these are primary studies.

And the Grossman studies, if you got to line four, the Grossman study has some problems with it. As Matt alluded to the response rate to the survey was very low. There were only 28 people who responded. They were not all physicians, over 50% of the people responding were from one institution, the University of Utah. And also there's conflicts there because the fact that 70% of the people involved do sentinel node biopsies, and really were not too interested. There were some people that were not MDs in there. They were interested in trying to decrease the number of procedures they were doing.

I want you to contrast the end and the value of that study if you go to slide five so the [Marson] study. And that study was done 589 almost 600 US board certified dermatologists, 65% of the people involved had experience already with the test. And you see the results of this, they used it in a T1 population where the Marson study shows exactly what your question was earlier, that people use the test to appropriately adjust management based on the results of the reassessment and prognosis to do this.

Now, this was a study that was done by the way also with less than 50%. The Grossman study was less than 50%, or 50% excuse me used for the Delphi procedure to get a consensus. So I think most of you though you put on papers and studies that usually you typically use a super majority of two thirds, three fourths, 80%. So there was a lot of strong minority viewpoints supporting the test that really weren't covered in that paper.

Let's go to slide six. And again, this was a different group of experts that was put together. These were expert dermatologist looking at the study, you can see from the slide again, I won't beat the details to death with this, but that they recommended that the test be included on all levels T1 and T2 for early stages for melanoma for this to do. Let's go on to slide seven, I want to talk about the Marchetti study again. But the important part of this is that there's one thing that's really wrong with the comments that are made in that paper.

And they say that when you include this with other independent factors and prognosis, that in fact, the validity of test and the strength of the test weakens, that's absolutely not true. Multivariate analysis, a number of these that have been published now show that this is an independent factor for predicting prognosis. So it just reinforces the importance of the test on this to do this. Now, let's go to slide number eight. This again, shows a bunch of new studies that were available for this to do this and you can see the difference in the number of patients, the number of doctors that we have a look at these studies in a very large way.

So I think that's an important emphasis of the fact that these are all new studies that have been published since the LCD was initially published, they need to be included in any revision that occurs to show that my view of the overwhelming evidence supports the strength and the validity and the utility of this test. Now number nine, if we go to slide number nine, Marchetti in that analysis, another problem with his analysis that he inherently recommends that all T1B patients get melanoma or get the sentinel node biopsies for this. And this is really not true.

And the other thing that's wrong with that study is they did not use the traditional endpoints that you typically use. In other words, they didn't use relapse recently, metastasis free survival, or melanoma specific survival for this. So that in itself was a problem too. Now, the other thing, let's go to slide 10. And I think if you use the same studies that are there, and you look at these studies that are there, it actually confirms the value of this in addition to sentinel node biopsy for prognosis.

Slide 11 to me is one of the most important study slides we go to that, because what that shows is that if you look at AJCC staging, which is typically what's used for staging for melanoma, if you add this data it's phase one, it's phase 2A, and you see look at this, you can see that a stage 2A patient will look; excuse me it's a stage one, sorry, it's a stage one patient is a 2B it will look like a stage two patient and vice versa. So having this data significantly changes assesses prognosis with a different way for this to do this. And it's really synergistic more than additive.

We go to slide 12. This is the slide I was referring to when you were asking the question before, these are six studies that confirm critically read and confirm clinical impact, which are both important, obviously, for this, but the clinical impact is quite clear, you get over a 50% change in management

based on this. And to me, this is perhaps one of the strongest arguments for the use of this test. So let me have slide 13 to summarize, it's clear that this test makes a difference.

It has critical utility. I use it on a regular basis. And I really hope that the LCD, if you do any revision in CLTD, you will improve all these other tests, all these other papers, excuse me, that show an improvement with the use of this test, and in fact, a more efficient use of resources. Because clearly with the data, you can obviate the use of sentinel node biopsy, especially on skin melanomas. And I think that to me is one of the most important things. So I thank you for your time.

Dr. Judy Volkar:

Thank you very much Dr. Rigel. Are there MolDX employees who have any further questions?

We will now switch gears totally and our final presentation is Scott Blackman. Speaking on Repetitive Transcranial Magnetic Stimulation in Adults with Treatment Resistant Major Depressive Disorder on behalf of BrainsWay.

Scott Blackman:

Again, my name is Scott Blackman, and I'm the director of market access for BrainsWay. And if you look at slide number two, I would like to thank everybody at Palmetto for drafting this coverage policy for transcranial magnetic stimulation in adults, particularly for your drafting of the OCD for these patients. The following comments are our recommendations for the policy. Next slide number three.

It states in the indications for coverage for major depressive disorder that TMS may be covered if prescribed and administered by a licensed physician who is knowledgeable in the use of rTMS and it continues. Our comment is that TMS is a very extremely safe outpatient procedure and a technician without any medical background is trained several hours to administer the therapy professionally.

The management of treatment resistant depression and OCD patients is complex and deserving of the highest trained clinicians available in the region. If the state allows advanced practice registered nurses to treat these patients independently, than they should also be allowed to prescribe TMS as well. If not, then TMS prescription should only be ordered by psychiatrists. The administration of the treatment should be performed by any certified technician.

Our recommendation is that nurse practitioners also be added to this statement with a physician. Slide number four please. Continuing with major depression under our initial treatment, that they have a confirmed diagnosis of severe major depressive disorder single or recurrent episodes. Our comment on stating severe major depression is that rTMS is indicated for patients with moderate to severe major depression.

Studies were conducted in moderate to severe major depression in patients who failed one or more medications in the current episode. Additionally, TMS is effective in patients with major depressive disorder with a range of depressive, excuse me depression symptom severity. Patient groups had on average moderate depression. Additional references will also be provided in our written comments.

Our recommendation is that we add the words moderate to severe and not just severe to the current episode. Slide number five please. Initial treatment states that one or more of the following resistance to treatment with psycho pharmacological agents is evidenced by a lack of clinically significant response to two trials of psycho pharmacological agents in the current depressive episode from at least two different agent classes for the inability to tolerate psycho pharmacological agents, as evidenced by two trials for psycho pharmacological agents from at least two different agent classes with distinct side effects.

Our comment is that we appreciate Palmetto's decision to reduce the number of medication trials from four to two by either a lack of clinically significant response or intolerable to psycho pharmacological agents. The literature, including the STAR*D study, and the recent update by Rush et all in 2020, demonstrated that patients with major depressive episodes, who actually fail to respond to their initial pharmacological treatment showed less and less response and remission with subsequent failed treatments.

Rush stated that after inefficacy with an initial failed SRI trial, only 21% of patients actually achieve remission. And 58% of patients achieve no meaningful benefit with a second step switch to another antidepressant. In DTMS pivotal trial, patients had a remission rate of 32% versus 14% Sham and response rate of 38% verse 31% sham after the initial four weeks of only 20 sessions.

Further treatment in the continuation phase actually showed, excuse me a 63% remission rate. Our recommendation would be to lower the number of failed medication trials to one failed medication trial. This would be consistent with the literature and the policies that are also published by Noridian, Novitas and WPS. Slide number six please. And a trial of evidence based psychotherapy under initial treatment known to be effective in the treatment of major depression of inadequate frequency and duration without significant improvement in depressive symptoms as documented by standardized rating scale that reliably measures depressive symptoms.

Our comment is that TMS is a very safe and effective treatment for patients with major depressive disorder. All United States FDA cleared devices for this treatment have been cleared for the use of patients who have failed to reach remission with one or more antidepressants. In three major pivotal trials for TMS, patients were not required to have failed multiple medication trials, nor a trial of psychotherapy in the current episode of depression.

2007, 2010 and 2015 major pivotal trials were published using the Neuronetics and BrainsWay TMS systems. The results of those studies show the treatment to be effective in depressed patients with both low and high degree of treatment resistance. These trials did not include burdensome restrictive requirements, such as documentation of failed psychotherapy sessions. Our recommendation is that we need to delete this unnecessary requirement and hurdle for a psychotherapy trial. It would actually delay and deny access to the safe evidence based effective TMS treatment for patients.

Slide number seven, intending under major depression initial treatment. The order for treatment is written by a psychiatrist, MD or DO who has examined the patient and reviewed the records. The

physician will have experienced administering TMS therapy, the treatment should be given under direct supervision of the physician, physician presently does not necessarily personally provide the treatment.

Our comment is similar as we stated earlier for major depression, we recommend that the treatment order and supervision of the TMS treatment also include psychiatric nurse practitioners. Slide number eight please. Moving on to Obsessive Compulsive Disorder. Excuse me TMS for OCD may be prescribed and administered by a licensed physician who is knowledgeable on the use of rTMS. rTMS may be indicated or outpatient rTMS may be indicated for patients with DSM5 defined OCD who have failed to benefit from initial treatment of their OCD.

Our comment is the same as earlier stated for nurse practitioners. Our recommendation would be to include the nurse practitioner in a statement to prescribe and administer rTMS. Under initial treatment, the order for treatment or re treatment is written by a psychiatrist. Again, our comment is the same as above is that nurse practitioners in the statement to write the order for rTMS treatment.

Under retreatment and utilization guidelines for OCD. Under retreatment, we agree with the retrieving parameters for both major depression and OCD. Our comment is that we agree with the statements regarding the numbers of the treatments 29 with extensions of two to four weeks based on clinical need with evidence and response and re treatment parameters of at least a 30% reduction in white box scores. This is consistent with a DTMS pivotal trial protocol by Karmi in 2019, as well as the real world evidence study by Roth et all in 2020, which demonstrated that patients achieved over 30% response after six weeks of treatment and over 50% response over the eight weeks of treatment. Additionally, written comments will be provided to find that out after this meeting. Thank you, and does anybody have any questions based upon the information presented?

Dr. Judy Volkar:

All right. Well, thank you very much Mr. Blackman, and thank you to all for commenting and participating in the open meeting for JM. This will then conclude our meeting.