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| First Coast Service Options, Inc.  JN Open Meeting |
| Thursday, August 10, 10 a.m.  Topics:  DL39367– Genetic Testing for Oncology |
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PRESENTATION

Mandy McGarvey

Good morning. I'm Mandy McGarvey, your WebEx host for today's open meeting. Before we get started, I want to remind everyone that this meeting is being recorded. At this time, I'm going to turn the meeting over to Executive Contractor Medical Director, Dr. Patrick Mann. Dr. Mann?

Dr. Patrick Mann

Good morning, everyone. I'd like to welcome everyone to First Coast's August open meeting. My name is Dr. Patrick Mann, Novitas and First Coast Executive CMD. Joining me today are my Novitas and First Coast colleagues, including Dr. Claudia Campos, Dr. Anitra Graves, Dr. Vinita Jackson, Dr. Gavin McKinnon, and Dr. David Summers. Please be aware that First Coast Service Options Inc. is recording this virtual open meeting to comply with CMS guidelines. By remaining logged in and connected via telephone or webinar, you acknowledge that you have been made aware that this virtual open meeting is being recorded and you are consenting to the recording. If you do not consent to being recorded, please disconnect from this virtual open meeting.

We are holding today's open meeting to provide you with another opportunity to present your comments. Open meetings allow interested parties the opportunity to present information and offer comments related to the proposed LCD and/or revised portion of a proposed LCD during the 45- day comment period. The proposed LCD topic for today's meeting is DL39367, genetic testing for oncology. During today's meeting, interested parties will make presentations of information related to the proposed LCD. Please remember, today's call is being recorded. And we request that all formal comments be submitted in writing before the end of the comment period on September 9th, 2023. We encourage you to submit full-text published evidence supporting your recommendations that have not been previously submitted. We appreciate and encourage all verbal comments relative to the proposed LCD. And please note that published peer-reviewed evidence submitted with your written comments will be considered a critical component in evaluating any changes requested.

At this time, I'd like to provide a brief overview of the proposed LCD for genetic testing for oncology. The proposed LCD is a LCD to cover all DNA and RNA testing as related to the field of oncology. This proposed LCD will cover the coverage requirements for testing submitted to First Coast for medical reasonableness and necessity. And please note that the LCD is not meant to be seen as a barrier to coverage for testing, but rather a mechanism by which the best and most well-vetted testing is provided to our Medicare beneficiaries. Let us start now with our first presenter. Presenting from Florida Urologic Society, we have Dr. Terrance Regan. Please go ahead, Dr. Regan, in stating any conflicts of interest.

Dr. Terrance Regan

Well, good morning. And thank you for having us. I do not have any conflicts of interest. Do we have my slides?

Mandy McGarvey

Thank you.

Dr. Terrance Regan

Oh, thank you. First of all, my name is Terrance Regan. I'm a urologist at Advanced Urology Institute. I've been a member of the First Coast Service Options CAC for, oh, almost close to 20 years. And I'm representing the Florida Urologic Society as well as the American Urologic Association, Large Group Practice Association, the American Association of Clinical Urologists. I want to thank all those at First Coast Services for having this open meeting and allowing to address this final proposed LCD. And I also want to thank First Coast Services for really trying to bring evidence-based medicine under the coverage policies for the beneficiaries. Next slide.

As you can see, this issue is very important to us. And we're going to be making comments today on the proposal to exclude the UroVysion FISH and Cxbladder test. These organizations are responsible for taking care of a large percentage of patients with bladder cancer. And the continuation and the ability to use these markers is very important to all the members of these organizations. Next slide.

A brief background. Bladder cancer, almost 83,000 new diagnoses a year and 16,000 deaths. In Florida there is 7,200 new cases. The Florida incidence is about 18.4 over 100,000. In Flagler County, the county that I practice in, the incidence is 24.5 over 100,000. I'm one of only two urologists who cover this county. And it is exceedingly important for us to be able to have good clinical resource management so that we can provide timely care to our patients. Included in this, the availability of tumor markers. So the fourth most common cancer in US men. Thankfully, most are noninvasive. But there is a high recurrence and small progression. But those who progress generally go on to have more aggressive. And their mortality is high. Next slide.

It has a protracted clinical course requiring ongoing management and often frequent interventions. Surveillance protocols are intensive and the compliance has been historically poor. Challenges remain with cystoscopy and the difficulty in discriminating between benign and malignant tumors, specifically carcinoma in situ. And cystoscopy is very highly operator dependent. Next slide.

These tumor markers have been covered by First Coast Services for some time. And they've been in the guidelines: the American Urologic Association and the Society of Urologic Oncology, these evidence-based guidelines whose expert panels use standardized methodologies and review all available evidence. It feels that these tumor markers should be indicated in some of the things that you see on the slide, including using UroVysion FISH as an early guide to predict response to intravesical BCG therapy. Equivocal cytology can happen as high as 21% of the time. And even high-grade tumors can have a negative cytology, so the ability to adjudicate these is highly enhanced with these tumor markers. Among the newer markers, specifically UroVysion, there's been a anticipatory positive test. Those whose tumor markers are positive are often found to have disease in the next year to two years timeframe. Next slide.

These tumor markers play a crucial role in the diagnosis and management of bladder cancer. They're incorporated into screening and management paradigms. They enhance detection of the carcinoma in situ in tumors not visible on cystoscopy. They identify tumors in the upper urinary tract. They predict recurrence. They monitor responses to intravesical therapy. In fact, a comprehensive analysis of nearly 3,000 manuscripts concluded that the addition of urinary markers to either cystoscopy or cytology provided the optimum sensitivity and specificity. Next slide.

Again, markers are currently included in existing guidelines in the American Urologic Association. Society of Urologic Oncology, again, have them in their guidelines so that a clinician may use the biomarkers to assess response to intravesical BCG in adjudicated equivocal cytology. National Comprehensive Cancer Network-- and I believe somebody is presenting from that organization. But speaking with some members who are familiar, they do not want to really decide between one tumor marker and the others. And they were not designed to come up with guidelines to adjudicate for those with atypical cytology, equivocal imaging, equivocal cystoscopy, etc. Next slide.

As mentioned, this proposed LCD is for genetic tumor markers for DNA and RNA. However, we believe that putting all these into one LCD is somewhat difficult and kind of beyond the scope of trying to add all of them in. Technically, these tumors are genetic tests. But they're not looking at specific genes, so they're generally not assessed by the ClinGen or the OncoKB registry. As mentioned, the NCCN guidelines don't necessarily cover the exact indications that these tumor markers are utilized in. Next slide.

The proposed LCD makes heavy reference to the low positive predictive value of some of these tumor markers. And that actually discounts the actual clinical practice which relies much more on their negative predictive value. In terms of Urovysion FISH, the positive predictive value may be low because white light cystoscopy can often miss tumors and carcinoma in situ, and enhanced light cystoscopy will often identify these. And as previously mentioned, the anticipatory positive tumors that arise, tumor markers can be seen as high as 40%. So the actual positive predictive value is probably much higher than the article cited in the response from First Coast Services. In terms of a negative predictive value, if you're looking at a low-risk population where you're trying to avoid intervention, then you're actually much more heavily reliant on a negative predictive value. I have spoken with urologists at Kaiser Permanente who are using these tumor markers for that very reason, to have excellent resource management, period, and to avoid intervention on those who have a very small chance of having malignancy.

The proposed LCD, as mentioned, really doesn't address the actual clinical utilization of these markers in terms of confirming presence or absence of cancer where the current clinical decision-making is somewhat difficult. We are not advocating replacing cystoscopy with this tumor markers or indiscriminate use of the tumor markers but allowing us to continue these tumor markers in the proper setting. Next slide.

Our concerns with the proposed LCD is that they're not completely supported by the American Urologic Association's clinical evidence in their guidelines. They may lead to worse patient outcomes and higher costs, they inhibit innovation, they ignore the actual clinical utility of these tests, they're in conflict with best practice recommendations from the US national urologic professional societies, and they may exacerbate existing disparities in bladder cancer care. Next slide.

This does have the potential to exacerbate disparities in access and outcome. There's already an issue, as previously mentioned, with access to urologists. Bladder cancer survival is dependent on the timely initial diagnosis and rigorous follow-up. Access to cystoscopy evaluation is not uniform and is strongly impacted by gender, race, social, and economic factors. That need for testing that obviated the need for travel was shown during the COVID-19 pandemic. And these disparities are further exacerbated by social, economic status, and race, with significant lower disease specific survival seen in African-American patients, those with lower social economic status and patients with Medicaid. Taking these tumor markers away, again, allows us to have proper resource utilization. Next slide.

There is a potential urinary markers may reduce morbidity and potentially reduce expenditures. Patients may be subjected to even more invasive testing and to adjudicated atypical cytology, with all their concerns. [inaudible] showed that the Cxbladder, 30% of patients may avoid further testing with tumor markers, and [Gamal?] showed that there can be savings up to $1,740 for those using urinary FISH and atypical cytologies and avoiding unnecessary biopsies. Next slide.

There were concerns raised by Novitas First Coast about some of the studies on these tumor markers, that there was a focus on male patients and population of European ancestry. But bladder cancer is three times more prevalent in males and much more prevalent in whites than nonwhites, and therefore these studies are likely to represent that geographic and race distribution. There was concerns that Cxbladder tests were not tested in the context of Medicare when 80% of Cxbladder moderate patient population was over the age of 60. Next slide.

There was concerns about funding and conflict of interest, the predominance of funding for studies by the markers' parent company, consistent with pharmacological device and other market industry study funding sources. And if that's reason for noncoverage, that would be problematic for all these devices, pharmacological markers. And--

Dr. Patrick Mann

Doctor, sorry to interrupt. Dr. Reagan?

Dr. Terrance Regan

Yeah.

Dr. Patrick Mann

This is just a quick 2 to 3-minute warning. We're going to be trying to keep people to 10 minutes because of the number of presenters.

Dr. Terrance Regan

Fair enough.

Dr. Patrick Mann

Thank you.

Dr. Terrance Regan

I've only got a couple slides left. Next slide. Next slide. Very quickly, some case scenarios that we see it in. I'm just a practicing urologists, and this are the cases I see. Elderly male patient with comorbidities, recent STEMI, on anticoagulation, history of CAS on surveillance cystoscopy. He's erythema and atypical cytology. Without these tumor markers, this patient is going to need to go the operating room for a biopsy. A negative tumor marker here avoids that. Next slide.

Similar. A Medicare age female with dementia, anticoagulation. No risk factors. Overall anticoagulated with CT scan suggesting possible malignancy. This is a issue of over anticoagulation. A negative tumor marker would avoid a cystoscopy and ureteroscopy. Next slide. So conclusion, urinary markers play a crucial role in bladder cancer diagnosis and management. This LCD does not properly address how these tumor markers are utilized. Guidelines support the use of tumor markers in the proper clinical scenario. The current guidelines do not address the proper usage of these tumor markers in the proper setting. These have been shown to decrease the cost and limit further invasive testing. We recommend comprehensive evaluation. And fair coverage decisions are needed in this. Next slide. And we believe that First Coast Service should continue to cover these tumor markers to enable proper resource utilization and challenging the patient population and care environment. If they are to be included in an LCD, they should be covered with appropriate use criteria, stakeholder input, and prior LCDS guidance. Next slide.

These are the references. Will be sent in the written response. I just want to thank First Coast Service again for allowing us the chance to participate in this open meeting. Thank you.

Dr. Patrick Mann

Thank you very much, Dr. Reagan. In one other note, the presentations will be held to about 10 minutes per speaker, just because of the volume of the speakers that have joined us today. The next speaker will be Dr. Clay Cockerell from Cockerell Dermatopathology. Please go ahead, starting with any conflicts of interest you may have. Thank you.

Dr. Clay Cockerell

Thank you. Next slide, please. Keep going. I do have one conflict of interest. I do consulting for Castle Biosciences. And we're talking today about, next slide, the LCD with relationship to test for skin cancer. Basically, MyPath Melanoma, DecisionDX-melanoma, and DecisionDX-Squamous Cell Carcinoma. And it seems that there's-- in the current proposal, it's looking to sort of potentially disqualify these tests based on preanalytic and analytic validity that has generally not been used to designate coverage for these tests previously. Next slide.

Basically, if you take a look at other tests that the NCCN have approved, basically they've utilized some of the standard preanalytic techniques and other routine types of criteria for CLIA, CAP, and others for this. But actually, we're looking at, in this LCD, using some different type of preanalytic validation that's more rigorous and doesn't really seem that it's really appropriate when NCNN and other organizations are using CLIA, CAP, and other types of criteria. Next slide.

Basically, this is used only by the-- independently by Novitas. This isn't something that has been used in the literature. It's not something that's being used by other organizations when they're approving tests such as this. If you actually take a look at publications in the literature, it's really almost impossible that they could use this type of rigorous sort of preanalytic testing that's proposed in the LCD, basically given the number of the word counts and limits imposed by journals. So the theory that mainly-- the fact that these aren't in the literature, it's really because the ability to do this type of testing wouldn't really make it through the materials and methods of most journals. Next slide.

If you take a look at CLIA, CAP, and the New York State Department of Health, these are also independent organizations that look at analytic validity. And they do this in a very robust way. I'm a practicing dermatopathologist. I've been practicing for over 30 years. We've had CLIA and CAP certification for a number of years. And basically, this is a very rigorous testing that we have to go through on an annual and sometimes even more than one time per year basis. They come in and do an actual onsite inspection. They have a checklist of all various things that they go through. So this is rigorous testing that's already kind of been imposed upon these tests already. Next slide.

And again, to sort of recap, CLIA is the certification organization that actually is the government organization that is used for this. And basically, Castle Biosciences has maintained their CLIA certification now for 15 years, since its inception. So all their tests are CLIA-certified tests. And these are very rigorous testing that is applied to these tests before they're actually utilized in clinical practice. Next slide. CAP is similar to CLIA. A little bit more rigorous than CLIA, but this also is a certification that Castle Biosciences has elected to do independently on their own, to get CAP certification. And they've been a CAP-certified laboratory now for 15 years. These also are inspections that come in-- a physician comes in and performs the inspection. They go through a very rigorous checklist. If there are deficiencies, there are certain periods of time that have to be met to correct those deficiencies. So it's actually a rigorous testing procedure that's already done for these tests. Next slide.

And then one other organization, the New York State Department of Health, is even more rigorous than CAP. And actually, this test is now approved by this method as well. So you've got CLIA, CAP, and New York State Department of Health that have all approved these tests. So it's not like these tests are being done sort of in a rogue fashion. These are being looked at very, very rigorously by multiple independent organizations. And to sort of say that there needs to be yet another type of testing that's even more rigorous than the ones that are used by the NCNN, this doesn't really seem fully valid. Next slide.

So if you take a look at this, virtually all of the tests that the LCD have approved previously, things like prostate cancer, thyroid cancer, breast cancer, and whatnot, those are basically CLIA-approved tests that are approved by the NCCN. The tests that the LCD really has chosen not to automatically basically approve because the NCCN has approved them undergo this more rigorous independent review that is not equivalent to CLIA, CAP, or the New York State Department of Health. If this type of criteria-- if these criteria were applied to the tests that are already approved by the NCCN today, breast cancer, prostate cancer, thyroid cancer, uveal melanoma cancers, they wouldn't be allowed to be approved. So you'd have to take them out of the NCCN inclusion if you applied these criteria to those. So I really sort of think that it's really somewhat inappropriate in a way to apply more rigorous testing than CLIA, CAP, and these others that are being used for NCCN inclusion for this test. It's almost as if it's sort of being discriminated against in a way. Next slide.

We personally think that the best way to go is to sort of have the same criteria used for all tests, not just using whether or not it's in the NCCN inclusion criteria or not. Basically use these types of criteria that the NCCN is using to approve their tests rather than to say, "Well, if it's not included in the NCCN, we're going to apply a more rigorous test than what the NCCN itself is using." So sort of just doesn't make a lot of sense to us. These are very valuable tests. They're really about the only molecular genetic tests that we have available in dermatology and dermatopathology. And I'm personally using them almost every single day in my practice, as are many other practitioners that do the kind of work that I do. It's very important for accurate diagnoses and prognostic information for Medicare beneficiaries. And we really think that we should apply the same type of criteria for this test as we use for the other NCCN tests, like prostate, breast, and other cancers. I think that's my last slide. Maybe one more, please.

So in conclusion, we think there should be some consistency and not really a bipartite pathway for approval of these. And it seems to me that these tests, like CLIA, CAP, and New York State Department of Health, are the ones who we really should be using for all of these tests. I believe that's the last slide. Thank you very much for your attention.

Dr. Patrick Mann

Thank you very much Dr. Cockerell. So moving on to our next presenter. I do need to double-check. We didn't see your name on the list. Robert Renjilian. Sorry if I'm making a mistake on your last name. Please correct me. Oh, I see you now on the list. So Dr. Robert Robert Renjilian is presenting from Interpace Biosciences. Please go ahead and provide your conflicts of interest and also a correction for the pronunciation of your name if I have unfortunately butchered it.

Robert Renjilian

Hi. Thank you. This is Rob Renjilian. Thank you very much. You did great in pronouncing my name. I am an employee of Interpace Biosciences. Next slide, please. Next slide, please. Key points that we'd like to make today is the fact that PancraGEN IMP and PathFinderTG are the same test. There seems to have been some confusion in the review of the data that's published, so we wanted to clarify that point. We want to share that the proposed LCD's analysis of evidence does not consider the full body of evidence that supports PancraGEN. PancraGEN has followed the classic pathway and supported by evidence from analytical validation, clinical validation, clinical utility, and cost-effectiveness studies. And we'll briefly share some of those with you today. PancraGEN has been covered by Novitas for 16 years, based on test-specific evidence that was not analyzed in the proposed LCD. PancraGEN is an important and long relied upon diagnostic tool for physicians to risk stratify the cancer risk for pancreatic cysts, and removal of coverage would remove beneficiary access to a resource that physicians have used to guide patient care for almost two decades. Next slide, please.

So a little bit of an overview. Interpace provides information to physicians to provide an assessment of malignancy risk. It all starts with a diagnostic biopsy that oftentimes is indeterminate in nature and poses the questions, "What do we do?" The test provided by Interpace Biosciences helps resolve that diagnostic uncertainty. As a bit of a history lesson, in 2004, RedPath Integrated Pathology was founded. They were the creators of the PancraGEN test. In 2007, Medicare started coverage for PathFinderTG. The test is as it was described today. It's 20 markers, 10 loci for tumor suppression genes and oncogenes, and the results are provided in the context of available clinical history and pathology information. In 2009, we received our New York State approval for PathFinderTG. In 2010, we received our original LCD. In 2014, RedPath was acquired by Interpace Diagnostics. In 2015, PathFinderTG was renamed to PancraGEN. There were no test-related changes. In 2015, we had a new LCD established. And in 2019, Interpace Diagnostics became a subsidiary of Interpace Biosciences. Next slide, please.

So to put all of that into context, a little bit of a logo farm here. It helps when evaluating all the literature that's available for PancraGEN. We are often referred to as RedPath or PathFinder or IMP. Point here is that RedPath equals Interpace Biosciences. Interpace Biosciences is a subsidiary of-- Interpace Diagnostics is a subsidiary of Interpace Biosciences. PathFinderTG is the same as PancraGEN, is the same as IMP, which stands for Integrated Molecular Pathology. Next slide, please.

PancraGEN is also a laboratory-developed test. The previous speaker did a great job in sharing the rigorous nature in which CLIA evaluates their test. We also are CAP certified. And we also have New York State health department of-- we have a laboratory permit from New York State. The bottom line here is that CLIA does not require publication of our analytical validation - next slide, please - which is why you can see that we have found a classic pathway. Analytical validation is done. The study has been conducted. It's just unpublished and has been provided to CLIA for their support and use of our test. We also follow, again, clinical validation. Our original studies in 2009, the PANDA study from Dr. Cooley, that was excluded. And the results should not be. It is part of the PancraGEN test. We also have included Dr. Al-Haddad and Dr. Farrell's publication. Dr. Farrell was excluded because PancraGEN was not mentioned. It actually was mentioned within the publication and with the CLIA validation study for us.

From a clinical utility perspective, Dr. Loren has a publication, and Dr. Arner. Dr. Arner was also excluded for not specifically mentioning PancraGEN. PathFinder was mentioned within his methods section, so we are including that here today as well. And from a cost-effectiveness perspective, Dr. Das did publish some publication in 2015. And there was no change in the test, so that should be included. So we have followed the classic pathway. Next slide, please.

And a little bit of what PancraGEN actually does. We actually provide risk stratification of pancreatic cysts. What you're seeing here is the consideration pathway that physicians go through. Patients present with either clinical symptoms or incidental findings through some other imaging technique. There are guidelines that are well established and in place to determine when an EUS-FNA is needed, when that EUS-FNA takes place, excluded, obtained. And there's a first series of tests that are done. Cytology is the gold standard. If you find a malignancy during cytology, you're done; you stop there. However, unfortunately, cytology has a very low diagnostic yield. We then try to triangulate in terms of understanding what type of cyst is out there. And there are various biomarkers that allow that. Amylase, CEA, and glucose, they help inform cyst type, but they don't inform malignancy risk. CEA and glucose is basically associated with mucin, which are associated with IPMNs and MCNs, which are known to have a higher risk of malignancy. But not all mucinous cysts become cancerous. And there's your diagnostic dilemma.

The molecular diagnostics provided by PancraGEN helps define malignancy risk further. And PancraGEN assesses the accumulation of the DNA abnormalities that occur, so that increase the risk, and integrates those results with clinical information. That's an important aspect of our test. It's not a molecular-only test. We are a molecular test that then integrates the clinical information and triangulates towards a decision. And we follow the clinical decision-making process of many physicians. However, not all physicians have the expertise to-- have seen so many pancreatic cysts to be able to do that and [inaudible] added value that we provide. Next slide, please.

So a little bit of an overview. As stated, PancraGEN is an integrated molecular pathology test. It does everything. If you look at the bottom, you have the molecular diagnostics component to the right, but we also review imaging, cytology, and the fluid analysis. So CEA, amylase, and glucose. That's then looked on a case-by-case basis by pathologists. So there's live eyes on those tests as well to integrate all those results, to come up with a defined risk assessment.

Our process aligns to clinical decision-making. We utilize DNA obtained from aspirated pancreatic cyst fluid. We use a Sanger-based testing platform. Sanger is the gold standard. That's extremely important in a pancreatic cyst because of the nature of how the FNA is obtained. Other digestive enzymes and everything from that area which can degrade the sample. Sanger is a little bit more able to handle some of that variability. Additionally, it's looked at by pathologists. And we've looked at 70,000 specimens, or almost 70,000 specimens, to-date. So there's a big and vast depth of experience that Interpace provides through our PancraGEN test in the market. PancraGEN looks at DNA quantity and quality. We look at point mutations in the oncogenes KRAS and GNAS, which are early markers for the progression of pancreatic cancer. We also look at loss of heterozygosity or tumor suppressor gene. Next slide, please.

So would like to take a moment to just briefly go over some of the data that was mentioned earlier in terms of the support for the PancraGEN test. One of the earlier studies was the PANDA study by Dr. Khalid. It showed that when there's a high presence of KRAS, it's actually diagnostic of a mucin cyst. And mucin is one of the indicators towards a high-risk feature. When they did the multivariate analysis that looked at DNA amount, KRAS [inaudible], they did find a correlation to malignancy. 96%. Next slide, please.

We're looking here at data from the Dr. Al-Haddad paper. Again, using integrated molecular pathology, which is looking at a combination of the molecular as well as CEA, growth of pancreatic duct diameter, and the size of the cyst overall. And it was able to risk stratify the cyst into four categories, benign, or statistically indolent, as well as statistically higher risk and aggressive. And this was done based on looking at all aspects, not just the molecular. When you have the benign or statistically indolent result, it's a low a risk that supports a surveillance strategy as opposed to an intervention strategy, consideration of surgery, when you're aggressive or have the higher-risk features. We'll talk a little bit about that in a moment. Next slide, please.

What you're looking at here is data from the Dr. Farrell paper. When you have worrisome features, these are features that are identified through imaging techniques. A mural nodule or main pancreatic duct diameter, cyst size, you have a change in the duct diameter or even symptomatology such as pancreatitis. These are worrisome features that would be currently evaluated by guidelines and that can lead to a surgical decision, which may or may not be needed. When you add in the DNA abnormality, such as elevated DNA quantity, tumor suppression gene, LOH, or also point gene mutations, you actually can further refine the risk stratification of those worrisome features. So we have found-- Dr. Farrell has found, excuse me, that when there's no DNA abnormalities, the risk is relatively low. When you have two or more of those DNA abnormalities that are picked up by the PancraGEN test, you actually increase your risk of malignancy. And if you have one DNA abnormality, you have an increased risk, but it's more towards the lower end. Next slide, please.

We also have data demonstrating the fact that the results from PancraGEN actually increases or has clinical utility. This is a study by Dr. Loren. When they looked at the PancraGEN test results versus the test results-- or excuse me, the guidelines - in this case, I believe it was the ICD guidelines - they actually saw that when there was a concordance to the guidelines, everything worked out great. However, when there was a discordance is where there was a value. When the marker showed high risk but the guidelines did not, 88% went to surgery. When the marker showed low risk but the guidelines showed high risk, there was a 55% prevalence rank. On the high markers, 57% of them are malignant. And when they were low- risk markers, 99% of them are benign. There absolutely was a benefit to the patient because patients that normally would have gone to surgery did not. It's a high-cost surgery. It's a complicated surgery. 0 to 15 percent of the surgeries result in a mortality, even in high-experience centers. Additionally, about greater than 40% of patients have a morbidity associated with it. So the fact that we could help inform a physician's decision to avoid surgery was very beneficial. And this is also a real-world study. We showed that the odds ratio for surgery versus clinical guidelines-- we redirected management at a higher rate than the guidelines did. Next slide, please.

Next study is from Arner. This also looked at molecular analysis of pancreatic cyst changes clinical management. In this case, molecular assessment changed management in 27% of the cases. What's very impressive in this dataset is that when the results of CEA were intermediate, they actually changed decision 40% of the time. So at the end of the day, it really was very helpful in surgical decision-making. Next slide, please. Cost-effective study by Dr. Das.

Dr. Patrick Mann

Excuse me. Sorry to interrupt. We'll give you one more minute to conclude, but you have reached the time limit, I'm afraid, so.

Robert Renjilian

Thank you very much for that update. If you can please go to the last slide. PancraGEN and PathFinder are the same test. Our studies indicate that the early version should not be removed. Full body of information is there. We've been covered like 16 years. And removing the coverage will take that benefit away, the patients. And we've been helping physicians guide patient care for over 20 years-- for 20 decades, excuse me. 2 decades. Thank you. I was rushing. Thank you for your time today. Appreciate it.

Dr. Patrick Mann

Thank you, Robert Renjilian. So moving on to our next presenter, presenting from the National Comprehensive Cancer Network is Dr. Crystal Denlinger. Again, if I mispronounced your name, please correct me. Please go ahead, stating any conflicts of interest, and then begin your presentation. Thank you.

Dr. Crystal Denlinger

Good morning. And thank you for the opportunity to speak to the proposed LCD on genetic testing in oncology. My name is Crystal Denlinger. And I'm the senior vice president and chief scientific officer at the National Comprehensive Cancer Network or NCCN. And I'm also a practicing medical oncologist. On behalf of NCCN, I'd first like to thank you for citing NCCN content as a mechanism for coverage. The NCCN clinical practice guidelines in oncology are transparent, continuously updated, and available free of charge for noncommercial use and through a multitude of health information or HIT vendors. As such, citing the NCCN guidelines for coverage ensures this policy will stay evergreen with the rapid evolution of the evidence. Today, I'll provide a brief background on NCCN, discuss the role of the NCCN Biomarkers Compendium, and provide feedback on the proposed LCD. Next slide.

NCCN is an alliance of 33 leading academic cancer centers in the United States working to improve and facilitate quality, effective, equitable, and accessible cancer care so that patients can live better lives. Next slide. NCCN develops authoritative information regarding cancer prevention, screening, diagnosis, treatment, and supportive care that is widely used by clinical professionals and payers alike. The NCCN clinical practice guidelines in oncology, or the NCCN guidelines for short, are a comprehensive set of 85 guidelines detailing the sequential management decisions and interventions across 218 algorithms that currently apply to 97% of cancers affecting patients in the US. More than 1,700 panel members participate in guideline development. And in 2022, there were more than 13 million downloads of the guidelines across web-based and mobile applications. Next slide.

As noted within the proposed LCD, NCCN guidelines are developed by multidisciplinary expert panels from NCCN member institutions in an evidence-based process that is integrated with expert consensus. The NCCN guidelines are updated at least annually, but quite often are updated more frequently as the evidence evolves, with a 184 total version updates across all guidelines in 2022. Next slide. The NCCN guidelines are considered the standard for clinical care and policy in oncology in the United States. The guidelines are believed to be the most thorough and most frequently updated clinical practice guidelines in any area of medicine and are the most frequently referenced clinical practice guideline in oncology. As previously noted, the guidelines are widely available free of charge for noncommercial use and through a multitude of health information technology vendors, are used by payers representing more than 85% of covered lives in the United States, and form the basis for insurance coverage policy and quality evaluation. Next slide.

The NCCN imposes strict policies to shield guideline development processes from external influences. The guidelines' development is supported exclusively by member institution dues and does not accept any form of industry or other financial support for the guidelines development program. There is a firewall surrounding the NCCN guideline processes, which includes financial support policies, panel participation and communication policies, guideline disclosure policies, and policies regarding relationships to NCCN's other business development activities. Next slide. A large body of evidence demonstrates that adherence to NCCN guidelines improves cancer care outcomes, including quality measures and overall survival, while also reducing the cost of care, including cost to the healthcare system and out-of-pocket costs to the patient. At the 2022 ASCO annual meeting, CVS Health presented two abstracts looking at total cost of care beginning with the first treatment and for the subsequent 180 days for colon and breast cancer-- for patients with colon and breast cancer in relation to adherence to NCCN guidelines. In both studies, there was a significant reduction in the total cost of care with concordance with NCCN guidelines. In the colon cancer study, this was most prominent and significant in the Medicare population. While in the breast cancer study, significant reductions were observed across both commercially insured and Medicare patients, with greatest reductions, again, see in the-- again, seen in the Medicare population. Next slide.

Also, at the same meeting, Agarwal et al. presented hypothesis generating data regarding survival outcomes and guideline concordant biomarker testing. In this single institution retrospective study of lung cancer patients seen over one year, comprehensive biomarker testing, as defined by the NCCN nonsmall cell lung cancer guideline, resulted in improved survival and effect amplified if test results were available prior to the initiation of first-line therapy. This difference was likely mediated by the use of targeted therapy, although factors contributing to survival differences were not reported. Large phase three studies of biomarker-driven targeted therapy-based treatments in numerous diseases, including lung cancer, colorectal cancer, and breast cancer, have demonstrated improved survival with appropriately utilized targeted therapy in the first-line setting as well as later lines of treatment, further supporting the survival benefits of knowing a tumor's biomarker profile at the beginning of treatment. Next slide.

NCCN guidelines and the derived library of compendia products help ensure access to appropriate care in clinical decision-making and assessment of quality improvement initiatives. The compendia library is a resource derived directly from the clinical practice guidelines to be used by payers, practitioners, or other healthcare entities for accessible, accurate, and appropriate information. The NCCN drugs and biologics compendium, or the NCCN Compendium, has been recognized by CMS and clinical professionals in the commercial payer setting since 2008 as an evidence-based reference for the establishment of coverage policy and coverage decisions regarding off-label use of anti-cancer and cancer-related medications, while NCCN has been recognized by CMS as a provider-led entity for the development of its Imaging Appropriate Use Criteria. Next slide.

The NCCN Biomarkers Compendium is also intended to be a resource for payers, providers, and healthcare entities that are navigating the rapidly changing evidence base for medically necessary biomarker testing in oncology. By consolidating biomarker testing information recommended within the NCCN guidelines, the NCCN Biomarkers Compendium is a resource for clinically relevant and succinct information that is linked directly to the NCCN guidelines to support testing decision-making in patients with cancer. The NCCN Biomarkers Compendium is designed to facilitate identification of biomarker tests recommended for use by NCCN guideline panels and is continuously updated in conjunction with the NCCN guidelines. The focus of the Biomarkers Compendium is clinical utility, with a goal of providing essential details for those tests recommended within the NCCN guidelines. All tests measuring gene or gene products used clinically for the purpose of diagnosis, screening, monitoring, surveillance, prediction, or prognostication, are included in the compendium. Next slide.

Launched in 2012 and updated in 2021 to have shared data fields with other compendia in the library, the information within the biomarkers compendia is extracted directly from guideline algorithms, principal pages, and footnotes, and all entries are reviewed and approved by the guideline panel pathologists or other panel members with expertise in the area. Information within the Biomarker Compendium focuses on the biology or abnormality of the biomarker being measured, in conjunction with utility in supporting clinical decision-making rather than on specific commercially available tests or test kits, with methodologic information provided only if it's included in the parent clinical practice guideline. With this resource, the NCCN Biomarkers Compendium aims to ensure that patients have coverage and access to appropriate biomarker testing based on the recommendations of NCCN panels. Next slide.

Dr. Patrick Mann

Dr. Denlinger, this is just a two-minute warning for you on the timing. Thank you.

Dr. Crystal Denlinger

Great. Okay. Yep. Okay. Yep. Next slide. So as you can see by this slide, where the biomarker landscape is rapidly changing in nonsmall cell lung cancer, there are a number of biomarkers for advanced or metastatic lung cancer. And when you are confirming the status of advanced disease, the next clinical consideration is the biomarker profile of the tumor. And then treatment is guided based on test results, which is a treatment paradigm replicated across all other disease sites. Next slide. The Biomarker Compendium will provide further details on the recommended biomarker. And this is a screenshot of the Biomarker Compendium, which is used by payers and providers. And it provides things like where the guideline is derived-- or the recommendation is derived from, the category of evidence and recommendation, as well as the test purpose and when to test and links to the guideline pages. And these fields can be customized to the user's needs to retrieve all of the necessary recommendations for a particular disease or gene-based search. Next slide.

This is just a screenshot providing the summary of the recommendations that come out of a search on the Biomarkers Compendium. And then the next slide. NCCN would like to, again, thank First Coast and Novitas for using continuously updated clinical practice guideline content to ensure patient access to appropriate biomarker testing, which can evolve to match the best available evidence. We have areas in which the proposed LCD-- where we would like to request additional clarity. The LCD notes that genetic tests for hereditary cancer syndromes, which are considered germline testing, may only be performed once during a beneficiary's life cycle. We anticipate that the intention here is to apply to each individual gene for which a beneficiary is tested, but we request clarity to confirm that as additional high-risk genes are identified, a beneficiary will have access to tests for those genes that they have not yet been tested for. Secondly, the LCD notes a limitation of the coverage is repetitions of the same genetic test on the same genetic material. We anticipate that this means that the same sample should not be tested for the same gene-based biomarker, but request clarity to confirm that this would not exclude the use of the same tissue to be test by a subsequent larger panel, in which some of the previous gene tested might have been included if there are additional relevant biomarkers not previously tested and would not exclude sequential tumor testing of tumor in the same patient over time to evaluate evolution of mutation or protein expression over the course of the disease and treatment.

NCCN thanks you for your time today and for your commitment to ensure beneficiaries have access to the highest standard of care, including access to appropriate biomarker testing. Please consider us as a resource. And we look forward to working with you to ensure that Medicare beneficiaries have access to quality, effective, equitable, and accessible cancer care. Thank you.

Dr. Patrick Mann

Thank you, Dr. Denlinger. Our next presenter is presenting from the University of Rochester and is Dr. Peter A. Prieto. Again, if I mispronounced your name, please correct me in your initial statements. And also, please provide your conflicts of interest. Thank you. Dr. Prieto? Are you having trouble with our audio?

Mandy McGarvey

He's connected via computer, but I'm not hearing anything. And his line is unmuted. I'll work with him to get connected.

Dr. Patrick Mann

Okay. We can move to the next.

Dr. Peter A. Prieto

You guys hear me now? You guys hear me?

Dr. Patrick Mann

Oh. There we go. Yes. We can hear you.

Dr. Peter A. Prieto

Okay. Sorry. Thank you. Well, yeah, thank you first for pronouncing my name right. You're one of the first that's ever done that. Secondly, thanks to the First Coast for the opportunity here. I am a surgical oncologist at the University of Rochester, who has evolved into also basically an immunotherapy, molecular therapist, and completed my training at MD Anderson. I have become very much interested in molecular testing for cutaneous oncology. And it's made a big difference in our patients. So I'm coming to you kind of from the front line. My disclosures I currently have decreased some of my clinical volume because of my interest and have taken a leadership position with a late stage biotech, Iovance. And I am a consultant for Castle Biosciences. Next slide.

So I'm talking to you today about cutaneous melanoma and gene expression profiling. And we're talking about a cancer that is on the rise, that continues to be on the rise. It's now the fifth most common cancer in America. This is a significant public health burden, especially for our Medicare eligible population. And if we look at just the sheer numbers, we're seeing that more than half of patients who die of this disease are diagnosed with early-stage disease at the time of diagnosis. So that's quite concerning. The median age of diagnosis is our target population. Again, 65 years of age, with ages between 55 and 64 having the highest reported instance. Current risk stratification is based solely on clinical pathologic features. And this really has limited accuracy and fails to appropriately identify a patient's risk for metastasis. And we have precedence for the lack of accuracy from reliance solely on clinical pathologic staging. We've seen this in other epithelial cancers. So why is it not the same in melanoma? 88% of patients who undergo a sentinel node biopsy-- and I'm a surgical oncologist. This is what I do for a living. And I will tell you this procedure is negative almost 90% of the time. And we're subjecting our patients to the burden of the procedure, which is not without a trivial amount of side effects-- nontrivial amount of side effects, including seroma, paresthesia. It costs the system tens of thousands of dollars. And it really fails, again, almost 90% of the time. And this is solely based on the fact that it showed a prognostic benefit from a study decades ago. And this is a procedure that was invented to provide prognostic information before we had genomic profiling. So it's 2023. We need to keep up with the times. The adoption of DecisionDX-Melanoma by treating physicians, including myself, is now becoming more common, thankfully. And we have incorporated it into many of our workflows at Rochester. And since 2013, over 10,000 clinicians have ordered well over 100,000 tests. Next slide?

The diagrams here show the problem. Again, a majority of patients present with early disease. And that sounds reassuring at first, but then you look at who succumbs to this disease and, again, more than half are stage 1 or stage 2 at the time of diagnosis. So many high-risk tumors are being misidentified as low-risk at the time of diagnosis. And the prognostic accuracy may be improved to inform patient management decisions if we can accurately profile a patient's tumor. And patients are twice as likely to survive if we detect asymptomatic recurrences. Why wait until the horse is out of the barn? We need to accurately profile our tumor so that we can efficiently and in a cost-effective manner identify when they develop recurrent disease so we can act fast, swiftly with the limited resources we have to provide the most benefit. Next slide.

As outlined by the NCCN guidelines and as we just heard from Dr. Denlinger, there is a recognition that prognosis drives the majority of treatment decisions. And that makes perfect sense. The risk for a positive sentinel node greater than 5% is estimated by AJCC. T stage directs decision for a sentinel node biopsy. The risk of metastasis, again, estimated by AJCC stage is used to drive treatment decisions for the frequency of follow-up, use of imaging for surveillance, and referral to specialty care. And we're seeing a broader and broader indication for involvement of specialties such as medical oncology with the new access point of immunotherapy for stage 2 disease. Which, by the way, the sentinel node is no longer the gatekeeper for. So this is an exciting time for systemic therapy in the melanoma space. Adjuvant therapy is becoming more and more available to patients. But again, is not without cost, is not without a trivial amount of autoimmune toxicity unlike sentinel node biopsy. We need to further stratify our patients and deliver the best available care to provide them with the best chance for outcome. So improvement in the accuracy of prognostication has an inherent impact on patient management decisions, outcomes, and really demonstrates the need for additional risk stratification, for which this test provides. Next slide.

We've shown before, again, across multiple validation performance studies, that total here over 9,000 patients, that whether archival or prospective, there is a clear and statistically significant stratification in patient survival based on class assignment, whether we look at all subclasses and combine cohort or just distinguishing between lower and high risk. And the consistency of these results really builds the confidence in the robust clinical data supporting the use of DecisionDX-Melanoma to provide prognostic information. Next slide.

Another study performed by John Vetto at Oregon Health Sciences University in 2021 was really interesting. It showed us that there was utility not only in early-stage disease, but patients who undergo a sentinel node biopsy, that this test actually outperforms what the sentinel node biopsy was tasked for in the first place. And that is the ability to prognosticate patients' kind of long-term recurrence-free survival. And sentinel biopsy is the standard of care, so why are we not improving on the standard of care? If you see here, the median follow-up for this study was 32 months. A sentinel node-negative patient, prospectively we could show a survival of 91% recurrence-free survival. With a low-class assignment of 1A, we saw a 97% improvement. And more importantly, we saw that the addition of Castle's DecisionDX class assignment to sentinel node status was really fascinating. Patients who had a positive sentinel lymph node, that is disease in their lymph node, did better than patients who had a negative node if the positive note patients had a low-class assignment. Again, showing that this perhaps could even trump the ability of what is now considered standard of care and really speaks to how much more accurate gene expression profiling can be. Next slide.

A more recent study which really is groundbreaking allowed Castle to collaborate with the National Cancer Institute and looked at over 4,600 patients to see, among an unselected group, could we identify patients who had been tested with DecisionDX gene expression profiling versus untested? Is there a survival signal? And it actually replicates what we've seen in previous publications. Again, that stratification by class assignment. Patients who were tested not only do better as we'll see, but this is further stratified to a statistically significant manner as illustrated by these Kaplan Meier curves by class assignment. Next slide.

Looking for patients, again, who were matched with patients who were untested, we saw that there was a dramatic effect on melanoma-specific survival and overall survival. And this has not been shown before in cutaneous oncology. Hazard ratios or measures of risk compared to a reference low-class 1A assignment, with the lowest risk by Castle, by multivariate analysis, had hazard ratios here-- as you can see, class 2B hazard ratios of 7. Seven times more likely to have an effect on your melanoma-specific survival with a high class assignment. That literally blew all the other factors out of the water and is independent via prognostic significance. Effects on overall survival, we see hazard ratios that are almost 2.4. So again, showing us that both class 1B and 2A and class 2B results are statistically significant and independent predictors of risk when compared to reference values. Next slide.

Dr. Patrick Mann

Dr. Prieto, I think you're going to need to come to conclusion pretty soon. You've got at least one more minute. So we've reached your 10 minutes.

Dr. Peter A. Prieto

Okay. So why don't we go to slide 10?

Dr. Patrick Mann Thank you.

Dr. Peter A. Prieto

Yep. So this, again, just highlights that we see a survival advantage among patients who are tested versus not. And now this has been published in the Journal of Clinical Oncology, Precision Oncology, showing that survival benefit. Next slide. So the review of the DL39363 shows basically the DecisionDX-Melanoma positive predictive value, which is the least stable metric across cohort studies. And we know that across multiple retrospective cohort studies, prospective studies, and multiple systematic reviews, that this test is able to identify patients' rate of recurrence, distant metastasis, and deaths. And this leads to clinically actionable information. Next slide. And we're just about finished here. The publications, as mentioned earlier, are listed here. And the draft LCD actually omits these levels of evidence when considering whether this should have coverage. And the last slide here. Appropriate management care for melanoma patients can be a significant burden on Medicare beneficiaries, and we need to align our treatment plans with the available information and the most accurate information to better stratify these patients. DecisionDX-Melanoma has met the criteria to be considered medically reasonable and necessary for our Medicare beneficiaries and really is essentially the right thing to do with the best technology we have in this personalized care of medicine. Thank you.

Dr. Patrick Mann

Thank you very much, Dr. Prieto. So our next presenter is coming from Desert Surgical Oncology, Dr. David Hyams. Again, please correct me if I get your last name pronounced wrong. And also give us any conflicts of interest that you may have. Thank you.

Dr. David Hyams

Good morning. This is David Hyams. I'm a surgical oncologist in southern Californian. In private practice as well as on the staff at UC San Diego. I have been in both academic and private practice. Involved in the development and work with a number of groups in gene expression profiling. My conflict of interest is that I currently do consulting work for Exact Sciences. And I am on the speaker's bureau for Castle Biosciences. So if we can start with the first slide, I think everyone on this call is familiar with the proposed LCD, which lists the following as primary pathway for genetic coverage and oncology, including positive review and inclusion by either the NIH ClinGen, positive review and inclusion by the Memorial Sloan Kettering-sponsored oncology knowledge base, or a positive review and inclusion by the NCCN guidelines committee stating that the test is either category 1 or 2A evidence. Since only NCCN guidelines review gene expression profiling test effectively, that means that approval for coverage of these tests would be at the sole discretion of the NCCN guidelines committee that reflects that particular disease state. Next slide, please.

I'm speaking today because I believe that requiring NCCN inclusion for test coverage is harmful to Medicare beneficiaries that I care for and slows availability of advanced, innovative tests. As the previous executive medical officer of the NSABP cooperative breast trials group, I had an opportunity to work with Genomic Health, a company that developed the first widely used breast gene expression profile, Oncotype DX, for breast cancer. That test was an interesting development and served as a very important model of how gene expression profile might develop. In the early days, it had significant headwinds. And this was due to the fact that it not only threatened the standard of care that was established by the NCI consensus conference of 2000, but it also challenged the clinical practice activities of much of the population of North American medical oncologists. It was approved by Medicare and insurance, however, long before it became part of what ultimately was NCCN guideline inclusion.

Requiring NCCN inclusion for coverage makes for a slow and arduous process, in my opinion, that can be heavily influenced by institutional and political biases. It's at odds with the 21st Century Cures Act and slows down and will ultimately prevent availability of innovative and advanced tests in oncology. I might point out that the quality of data supporting the development and validation of the DecisionDX-Melanoma 31 gene expression profile, as well as the 40 gene profile for squamous cell cancer, would have been approved based on the kind of evidence that was available by Oncotype DX at the time of Medicare coverage and ultimately NCCN guidelines inclusion. Next slide.

Perhaps most concerning to me about relying on NCCN guidelines as the primary arbiter is the fact that there's inconsistency in the level of evidence that's been required for gene expression profiling in different disease states. Evaluation of the NCCN cutaneous melanoma panel is misaligned with published evidence. The NCCN nonmelanoma skin cancer panel hasn't yet included any discussion of molecular testing, which I have a hard time believing can be construed as either negative or positive. And I think review is needed. And finally, the NCCN does not appear to meet the specifications and documentation of transparency outlined in the LCD. All of this creates disparities, inequity, and difficult access for patients with melanoma and squamous cell cancer compared to other disease states in which prognostic gene expression panels have been adopted by the respective NCCN panels with similar or even less evidence. Next slide.

The next slide summarizes some of these differences. Because of time, I won't go into the details, but they're available to your group. Looking at the issues in both breast and prostate cancer, one can see inconsistencies in both approval categories and review that exist even within the disease states themselves, not to mention between these disease states and cutaneous malignancy. I might point out, in breast cancer, that Oncotype is the only NCCN-validated test. And yet there are several assays that provide predictive and prognostic information that end up in the guidelines. The second most common breast cancer test in the US, which is MammaPrint, has not been NCCN validated and yet is listed as NCCN category 1. With the exception of the very large NCI-sponsored prospective trials that were not conducted by the assay manufacturer, only Oncotype and, in Europe, MammaPrint were subjected to prospective randomized clinical trials. But in each of these cases, these huge, very expensive studies were proof of principle and will likely not ever be repeated either by the NCI or other manufacturers. They're just not practical. Our patients, my patients, cannot wait for another $100 million trial that might never be conducted to gain the benefit of gene expression profiling in breast cancer, cutaneous melanoma, or any other oncologic disease states. We need to use available data. We need to think carefully and rationally about what that data means. Next slide.

The next slide simply illustrates what we've said before, which is that if we look at several assays, including the Decipher prostate assay, Oncotype DX breast, DecisionDX-Melanoma, and DecisionDX-Squamous Cell Cancer, Decipher prostate was approved by Medicare in 2015 with 11 published studies available, including 10 clinical validation and 1 clinical utility study. However, it took three more years until the test was included in the NCCN guidelines. Oncotype was approved by Medicare in 2005 with only 1 published study, a prospective retrospective study, the NSABP 14, and 4 poster presentations. And it received inclusion in NCCN guidelines only three years later, in 2008. DecisionDX-Melanoma was approved by Medicare in 2018 with 15 published studies available, including 9 clinical validation, 5 clinical utility, and 1 analytic validity study and is still not included in the NCCN guidelines. DecisionDX-Squamous Cell Cancer was submitted to Medicare in 2022 with 9 published studies, including 3 clinical validation, 3 clinical utility, and 1 analytic validity study, but has still not received review by the NCCN guidelines committee.

Dr. Patrick Mann

Dr. Hyams?

Dr. David Hyams

Yes.

Dr. Patrick Mann

Dr. Hyams, this is Dr. Mann. You have about a minute left, so this is your one minute.

Dr. David Hyams

So in such a case, I guess what I'd like to do is I'll do what Dr. Prieto did and skip to the end. If you can skip to the last slide. I'd like to stress that there are inconsistencies between LCD coverage criteria and the NCCN review and inclusion process. Despite the very nice overview presented earlier this morning, NCCN does not provide detail and evidence reviewed and analysis of evidence or adequate rationale for determination of use. The level of evidence, standards for guidelines inclusion vary between disease state panel significantly. And NCCN guidelines do not meet requirements for consistency of test evaluation, transparency, or documentation standards across disease states and even, of course, between disease types. In particular, the 40-gene profile for squamous cancer has no evidence reviewed by an NCCN guidelines committee for squamous cell cancer. And this shouldn't be interpreted as inclusion or noninclusion because it hasn't even been reviewed. And yet, data has been provided and available since 2022.

In the end, I would echo what Dr. Prieto said earlier, which is that when I see patients with malignant melanoma, a disease in which our current staging is significantly inadequate, in which a third of the patients that are biopsied in the United States have a transected base making Breslow thickness inaccurate or unattainable, in which ulceration can be confused with excoriation from an immunogenic tumor, those are the key factors we have in AJCC staging which gives us information about prognosis. And that information isn't available, for up to a third of patients, in a reliable manner. As a result, being able to utilize gene expression profile and to make decisions for my patients about whether or not to include a sentinel lymph node biopsy or whether or not a patient should receive adjuvant therapy with a significant risk profile nonetheless for stage 3A or 2B disease is very, very difficult without the objective information that's been made available and well documented through both the 31-gene expression profile in melanoma and increasingly with the 40-gene expression profile in squamous cancer. Thank you very much.

Dr. Patrick Mann

Okay. Thank you very much, Dr. Hyams. Moving on to our next presenter, presenting from Advanced Dermatology and Cosmetic Surgery, Dr. Etan Marks. Again, if I pronounce any part of your name incorrectly, please correct me. And then please start with your conflicts of interest. Thank you.

Dr. Etan Marks

Good. Thank you, Dr. Mann, and thank you for having me here. So I wanted to start by saying that I am a consultant for Castle Biosciences, but I wanted to comment on this for free because as other people have been discussing the clinical ramifications for the DecisionDX-Melanoma and SCC, I wanted to go through some of the laboratory factors that were discussed in the LCD. Next slide, please. So the proposed LCD does a monstrous job of reviewing tons of literature. I understand how difficult it is. But I think it does an insufficient job of reviewing gene expression profile testing in general because the concerns raised in the LCD demonstrate a lack of knowledge of the relevant background studies of how gene expression profile tests work and how they were validated up to about 20 years ago. There's only one reference supporting the need for a role of the long list of preanalytical variables that it discusses. The analytical validation requirements appear to be based on opinion more than adherence to actual published standards for the gene expression profile testings. And moreover, there are foundational publications that support the methods to perform gene expression profiling, including the appropriate methods for controlling for preanalytical variables are not cited by the LCD and preclude exhaustive independent demonstration of the impact of these preanalytical variables by individual tests. There are several references that we're going to have that talk about these as well at the end. And really, for any molecular approach, when using well-established, cited methods, it's not necessary to reinvent the wheel. Gene expression profiling has been used in many different situations. And Castle Biosciences shouldn't have to show that gene expression profile testing is a valid technique. Next slide, please.

The conclusion is drawn from the single reference to justify several requirements for this detailed evaluation of the preanalytical factors doesn't even seem to be really supported by this publication. For example, that samples were stored for up to 12 months, and they didn't show a significant decline in the PCR performance. Although it did show increasingly fragmented state of the DNA, it still showed that even with that fragmentation, gene expression profiling still worked. The storage of the blocks, which is what Castle used in their validation studies, showed that it did not affect the RNA quality. Even these over-fixed specimens that the study talks about showed marginally fragmented RNA with a maximum amplicon length for samples fixed for 72 hours were 400 to 600 nt in most cases, nucleotides. So that's well above the range that DecisionDX-Melanoma and SCC use even. And FFPE samples were shown to be stored 1, 2, 4, 7, even 10 years, with no correlation between the age of the sample and RNA yield. Even though they did show different fragment size, but they showed the RNA yield was still acceptable. And they also showed no clear correlation between RNA fragmentation and CT values. So it showed that basically RNA can be extracted from aged blocks, FFPE, formalin-fixed paraffin-embedded blocks, which is what a lot of samples for these types of tests use. Next slide, please.

The LCD insufficiently reviews publications establishing methodology for reliable RNA extraction, right? So this foundational study done almost 20 years ago by Cronin et al describes the variability inherent in processing of surgical tissue specimens and that the appropriate correction for this is used by reference genes. Meaning that when I have RNA extracted, even from an older specimen, as long as I have reference genes, this study conclude that normalization of RNA using reference genes with a geometric averaging effectively negates any type of different specimen collection. Right? And from the study itself, I just wanted to read this paragraph, but I'll just keep it to the bolded area, "The correction is routinely accomplished by normalizing raw expression value relative to a set of genes that vary little in their median expression among different tissue specimens, aka reference genes." So when you do gene expression profiling, you use a reference gene-- everybody who does gene expression profiling uses a reference gene to make sure that the genes that they are quantifying are appropriately being amplified. Next slide, please.

Archival FFPE tissue is routinely used for validation of gene expression profile testing as well as most other DNA-based tests that work on surgical pathology specimens, right? The LCD states, "Material used must be comparable to material tested in the clinic," and goes as far as to state, "One cannot legitimately develop a test for blood using only urine, tests for female using males," and so on. But that doesn't really correlate to here because we're using formalin-fixed paraffin-embedded tissue. It's just, is it one year or is it two years old? Is it five weeks or is it one year? Saying that an older FFPE block is similar to comparing blood to urine completely misses the analytical validity here. It doesn't really correlate in any way. This assessment also is in direct contraindication to later criticisms which say insufficient follow-up time, which wouldn't be possible because you'd have to use archived tissue. And it would invalidate all tests that are developed and validated in retrospective studies.

Lastly, something that's closer to my heart, which I've done in the past, is I've used archival FFPE tissue. And it's been shown to be comparable to newer FFPE. What I have seen is that if I had a 15-year-old block, I do have more failures. But I use reference genes to make sure that I know that the failure shouldn't be included and shouldn't be reported. We have DNA-based tests, we have RNA tests. And frequently, there will be reports that DNA or RNA was not able to be amplified and therefore cannot run the test on this specimen. But just because a block is older doesn't mean that it doesn't work. Specifically, for T cell receptor gene rearrangements, I've seen where they have no time limit. And even if I want to use clinically a block that's five years old to find out if it's lymphoma, that's considered clinically valid. Next slide, please.

Dr. Patrick Mann

Just to give you a heads up, this is your one-minute warning. Thank you.

Dr. Etan Marks

Okay, so let's go to the last slide, then. To summarize, I just wanted to say it looks like this LCD has a misconception that GEP is actually based on a single cell rather than a whole tumor tissue sample for macrodissection, which I wanted to just say for GEP, you're not trying to develop for a single test. It's the tumor microenvironment. The microenvironment is testing all of the genes expressed in the entire microenvironment. And saying that this is specifically for a single cell misses the whole point of GEP in general. This is not a FISH-based test where I'm looking at individual PET cells. I want the entire gene expression profile of the tumor microenvironment. So that criticism didn't make any sense to me. It also misunderstands the selection of utility of reference genes, saying that for some reason, reference genes don't validate a specimen. Inappropriate concern regarding preanalytical variables and protocols that are not under the regulatory control of molecular diagnostic procedure, which actually makes GEP tests more robust. So different hospitals will be using different procedures for specimens in surgical pathology. Lack of recognition of widespread use of archival FFPE tissue to develop and validate the GEP tests and inappropriate concern regarding RNA isolation and integrity from FFPE tissues. So these are just examples of significant issues that I specifically had when I was looking over this LCD for the criticisms of the preanalytical. And the thing that really-- it showed a lack of understanding of what the gene expression profile was telling us and how it was, as the the previous presenter showed, that this clinical validity has really been helpful for all these patients. And just on a personal note quickly, I have seen many of these tests be performed on patients that help the dermatologists and oncologists manage their patients and lead to better patient outcomes and prevent from more expenses and lead to better outcomes. Thank you for your time. I appreciate it.

Dr. Patrick Mann

Thank you very much, Dr. Marks. Moving on to our next presenter, I believe, and please correct me if I'm wrong, that Robert Renjilian is going to be presenting on behalf of Dr. Stephen Steinberg for Boca Raton Regional Hospital. Is that correct?

Robert Renjilian

Yes. Hi. That is correct. Thank you. This is Rob Renjilian. I'm an employee of Interpace Biosciences. So I believe Dr. Steinberg-- I'm presenting his slides, so I'll do my best. Dr. Steinberg wanted to point out that there are definitions and assumptions within the LCD that don't necessarily align to the risk stratification of pancreatic cysts, specifically within the definition of substantiated suspicion of cancer. For the purposes of this LCD, radiologic suspicion of cancer is not considered substantiated. Additionally, within one of the definitions, normal results had to be from [histolic?], cytologic, or flow cytometric examination. All these processes are not followed. Cytology is the gold standard. However, oftentimes, it has a very low diagnostic yield, and it doesn't provide any value. Flow cytometric and examination is not done for pancreatic cysts historically. And the whole idea of radiologic suspicion is what drives the process of clinical decision-making. So he believes that these definitions and assumptions need to be relooked at. Next slide, please.

Overall, there's a pathway to the clinical decision-making process. Usually, an incidentaloma is found due to some sort of imaging. Or there could be a presentation of symptoms, which leads to a consideration that there might be something going on. So then to further move towards a diagnosis, there are further imaging studies. Ultrasound, MRI, MRCP. Guidelines will indicate whether or not an EUS-FNA is taken. The fluid from the FNA is then evaluated. They try cytology. Again, a low diagnostic yield. They'll do fluid chemistry in an attempt to assess tumor cyst type, which has associated risks with it, but it's not 100%. And then tumor markers, including microdiagnostic tests, can also be used to further delineate the situation, which then informs the management decision as to whether to do surgery or to go into a surveillance program. Next slide, please.

Okay. So here, I believe he is trying to indicate that cytology has a very high specificity but a very low sensitivity for malignancy. There are limitations, such as interobserver variability, insufficient cellularity, and again, contamination from the gastric duodenal epithelium. On the bottom right, I believe that's the Brugge study, which was the classic one that identified 192 milligrams from a liter as being indicative of a mucinous cyst. An important point here is that there is no correlation between mucin and malignancy. It basically just identifies the cyst type. But that cyst type is not definitely defined as being cancerous. Next slide, please.

Here's an overview of sort of the decision process to identify cyst types. You have nonneoplastic cysts and true epithelial cysts. Everyone's excited when there's a pseudocyst or a serous cystadenoma because there's no malignancy potential. However, when you have an IPMN or an MCN, they're mucinous cysts, and they do have malignancy potential, along with SPNs and cNETs. So really trying to understand what they are. Mucin is a diagnostic principle within the guidelines because it identifies an IPMN or an MCN, which do have malignancy potential. But it's potential and not necessarily definitively cancerous. So that's why additional deeper analyses are needed, such as molecular diagnostics. Next slide, please.

There are initiation mutations such as VHL and C-T and [MB1?]. These are very indicative of the nonepithelial cancer cells, the ones that don't have malignancy potential. You also have initiation mutations such as KRAS or LOH, loss of heterozygosity. Those are indicative of MCNs and IPMNs with great specificity. Next slide, please.

And what we're looking at here, I believe, is an overview of the various guidelines that are in the market, or that are available to physicians to help advise treatment decision pathways. The point here is that there's many of them. They all rely on similar things such as symptomatology, imaging, diagnostics, and some simple serum-based tumor markers. Also, some of them use high-risk features or worrisome features. Again, those are established through clinical diagnosis, and they're not necessarily-- next slide, please. Yeah. All right. So what he's saying here is that the guidelines underperform in clinical practice. The guidelines are in place. They are followed. Everyone does their best in following them. However, it's an inexact science, and therefore everyone needs to triangulate looking at all available information. And some of that information does include the results of molecular diagnostics. Next slide, please.

This fluid molecular markers and determination of malignancy-- this is data from Singhi that talks about KRAS and GNAS. Again, those are early markers in the progression of pancreatic cancer. They show up early. They're indicative of mucin. And they can really have-- when looked in the context of tumor suppression, alteration, or LOH, it does have a very high specificity and a good sensitivity. Next slide, please.

This is information provided by Bell. It's a recent publication, I believe, that looked for clinical follow-up. 11 years. So it's 11 years-- or up to 11-year data. And what you're looking at, the left, is the ACG guidelines, which had eight false negatives. And if you look at the results of PancraGEN , which is on table six, there were six-plus negatives. Now, the result here is PancraGEN test was able to better refine the decision in at least two of those cases. Again, this is over 11 years. And in that study, over that 11-year time period, there were no additional case of adenocarcinoma. So when the test made the call to solve is correct. If you go to the next slide, please. Okay. The importance of even of those two sort of-- ability of PancraGEN to further refine even just two of those samples in that study was the fact that there is high risk associated with pancreatic cancer. Even in well-established and well-experienced hands, there's a 0 to 15 percent risk of mortality from the surgery alone. And it also has a very high morbidity rate of 40 percent. So missing that, too. There is reduction in cost. There also is just a better patient outcome. Next slide, please.

Within the guidelines, I believe section four, it says that diagnostic use cases, you can-- as a society, guideline will support reimbursement. So the next slide, please. Okay. So as discussed, or previously, the point Dr. Steinberg was making was the fact that the guidelines are imperfect. They're known to be imperfect. And they're in the process of being updated. The updates do include the assessment of molecular diagnostics. And he believes that they will be included within the new guidelines that are in the process of being updated. And his point was that removing reimbursement now will impact the future availability of this important diagnostic information. Thank you.

Dr. Patrick Mann

Thank you very much. Now moving on to our next presenter. From Baptist Medical Center, Dr. John Nieto. And again, please correct me if I have mispronounced your name. And please present your conflicts of interest. Thank you.

Mandy McGarvey

Dr. Mann, he was on, but it looks like he's dropped off. We'll work on getting him back on.

Dr. Patrick Mann

No worries. So while we wait for Dr. Nieto to come back, we will move on to our next presenter, Sarah Thibault-Sennett. Again, if I've mispronounced your name, please correct me. She is presenting on behalf of American Clinical Laboratory Association. And please present your conflicts of interest. Thank you.

Sarah Thibault-Sennett

Hi, can you hear me?

Dr. Patrick Mann

Yes. Yes. We can hear you.

Sarah Thibault-Sennett

Oh, okay. Great. Sorry, I had some issues unmuting. All right. So I'm Sarah Thibault-Sennett, the senior director of reimbursement policy for the American Clinical Laboratory Association. In terms of my conflicts of interest, I work for ACLA and represent a number of laboratories who are within the Novitas and First Coast jurisdictions. Okay. So ACLA is the national trade association representing lead laboratories across the country. And we're in the process of preparing detailed written comments to submit by the September 9th deadline. During the open meeting, I would like to highlight two of our main concerns about the draft LCD. First, the genetic testing for oncology draft LCD lacks a pathway for coverage if a test does not include it in one of the three knowledge databases. While we appreciate that Novitas and First Coast have indicated that individuals can request an LCD reconsideration for coverage of a specific test, this option is neither clear nor transparent. For instance, it is unclear what the timeline would be for the review and response to reconsideration requests and what, if any, opportunities will exist for the public to provide input on the decision for reconsideration. It is problematic that a test that is not included in one of the databases will be noncovered without any review of the evidence until a reconsideration request is submitted and considered. ACLA stands by its position that the LCD process is the only permissible basis for establishing a policy of noncoverage of a clinical diagnostic laboratory test as determined by the Social Security Act and the Medicare program instruction. We recommend that Novitas and First Coast modify the LCD to remove the limitation that tests not included in the three identified databases are presumptively noncovered.

Second, the draft article lacks many of the ICD-10 codes that are included in the current articles, which are slated to be retired when the genetic testing for oncology LCD becomes active. Removal of these ICD-10 codes will prevent access to standard of care and medically necessary testing for Medicare beneficiaries in the Novitas and the First Coast jurisdictions. As one example, the draft article does not include the not otherwise specified or NOS ICD-10 codes that currently have coverage under active articles. While more specific codes for standard and usual anatomic locations and gender can be used for cancer diagnosis, the NOS codes are the most appropriate diagnosis codes in some clinical cases. Further, the use of NOS codes has been supported multiple times by the Centers for Medicare and Medicaid Services. Additionally, the NOS codes are frequently used for late-stage cancer diagnoses when there are multiple instances of cancer in an organ system. As this policy will be used for patients with late-stage cancer diagnoses, we are very concerned that this will have a negative impact on patient access to appropriate testing. Not only does exclusion of the NOS codes from the article go against current CMS guidance, but it also will create numerous discrepancies for claim submissions and confusion regarding coverage as the NOS ICD-10 codes are associated with FDA-approved therapies.

As a second example, the ICD-10 codes related to remission, specifically for hematological malignancies, are missing. In many hematological malignancies, remission is determined following appropriate DNA testing. In these cases, the DNA testing is performed to establish remission status with the ICD-10 code updated to remission if it is consistent with the test results. As the policy is written, the standard of care tests to establish remission for hematological malignancies will not be included for coverage. Additionally, the exclusion of the remission codes will prevent genetic testing to monitor a condition, such as minimal residual disease testing or MRD. While Novitas and First Coast have stated that the policy was written to permit MRD testing, we believe the lack of remission-related ICD-10 codes will prevent tests from being used for this purpose. We recommend that additional ICD-10 codes be added to the billing and coding genetic testing for oncology article prior to the implementation of the policy.

As part of our full written comments, ACLA will be providing a full [red line?] of suggested edits to the ICD-10 groups from the coding and billing article. Beyond these two issues discussed today, ACLA is in the process of identifying further recommendations for the policy with our members and will be submitting full written comments on these items and others. Thank you for the opportunity to share our concerns during this open meeting. And we look forward to working constructively with Novitas and First Coast to address the concerns and recommendations for this draft LCD.

Dr. Patrick Mann

Thank you very much for your presentation. So as for Dr. Nieto, it sounds like he is unable to present today but will be presenting at the Novitas open meeting, which is tomorrow. At this time, since we have no other presenters, I would like to ask if any of our CMDs have any questions. And we'll give a brief pause. Hearing no questions, I will move on to say thank you for all of our presenters for attending and presenting their concerns and information. And please submit any comments you have in writing before the end of the comment period, which ends on September 9th, 2023. We encourage you to submit full-text published evidence supporting your comments and full-text published evidence that has not been previously submitted as can be found in the bibliography of the LCD. With this, the meeting is adjourned.