Molecular Testing for Risk Stratification of Upper Gastrointestinal Cancer CAC Meeting Transcript

Dr. Angela: We have just begun the recording of this CAC meeting in compliance with CMS. For the record, prior to doing so, I announced that Palmetto GBA would make an audio recording of the CAC meeting and consent it on behalf of Palmetto GBA. I also announced that I, Dr. Angela Charnot-Katsikas will be facilitating the session today in the place of Dr. Gabriel Bien-Willner Thank you again for joining us this afternoon, as we discuss molecular testing for risk stratification of upper gastrointestinal cancer. We are joined today by our subject matter experts in the field. I would like to take this opportunity to introduce them now and when I do introduce your name, please announce yourself so that I know actually have joined the call. I would appreciate that very much. We have Dr. Raul Pannala, an associate professor of medicine at Mayo clinic in Arizona. Dr. Pannala, have you joined the call?

Dr. Raul Pannala: Yeah, give me just a few.

Dr. Angela: Wonderful, welcome. Dr. Kenneth Wang. We heard you just a moment ago. Dr. Kenneth Wang is the director of the advanced endoscopy group and esophageal neoplasia clinic, and a consultant in the division of gastroenterology and hepatology Dr. Wang. Welcome.

Dr. Kenneth Wang: Thank you.

Dr. Angela: And we have Dr. Robert Odze, a former professor of pathology and chief of GI pathology at Harvard medical school, and now head of a medical consulting company, Dr. Robert Odze, have you joined the call?

Dr. Robert Odze: Hi, I'm here. Yeah. And it's pronounced to odds like odds and ends.

Dr. Angela: Ah, okay. Thank you for correcting me.

Dr. Robert Odze: Good afternoon.

Dr. Megan Landsverk: So, it looks like we just lost Dr. Katsikas. This is Dr. Megan Landsverk. I'm also with Palmetto. Can everyone hear me? Okay.

Dr. Angela: No worries. This is a group effort everyone. Dr. Steve, can you introduce yourself please? I don't have you on the list, and my apologies.

Dr. Stephen Meltzer: I guess I got invited, but maybe I didn't properly ascent to it. Stephen Meltzer with a pH from Johns Hopkins.

Dr. Angela: Welcome Dr. Melter. This is a process whereby when our panelists have undergone seat of some questions and have also provided some conflicts of interest disclosures and things like that. So, although we certainly appreciate

your presence. If you haven't provided those, that information, please send it as soon as possible.

Dr. Stephen Meltzer: Okay. Yeah. Can you send me an email and I'll send it?

Dr. Angela: Sure, we will do that. So, thank you email for joining us.

Dr. Stephen Meltzer: Do you need my email address?

Dr. Angela: Yes. Why don't I go ahead and take that down. Go ahead. Thank you everyone for joining us, our administrator will make sure to mute anyone who is not speaking. And please also mute yourselves just in the event that we have another technical glitch. So why don't we go ahead and begin.

As you know, we would like to discuss the evidence available regarding molecular testing for risk stratification of upper gastrointestinal cancer. We have provided our subject matter expert panelists with some questions for discussion. Panelists, as you respond to each question, we also ask that you rate the confidence in the evidence being utilized for each key question, using a scale from one to five, one being low confidence and five being the highest confidence. And we will note your ratings. So why don't we begin. Each of our panelists will have the opportunity to respond to each question, and we will begin with the first question and I will ask the panelists individually for their responses and then panelists, if there is something you want to add, please, by all means, go ahead and do so. So the first question is, is there sufficient data to use molecular testing, to identify and risk stratify patients with Barrett esophagus with low or high grade dysplasia? So, if I can ask Dr. Pannala to take the first response.

Dr. Raul Pannala: How would you like it? Do you want me to just give you a number or just kind of go over my thoughts?

Dr. Angela: Please give us your thoughts about the data regarding the ability to risk stratify these patients and to lower high grade dysplasia, but also please do provide again the confidence and the evidence for the response. So again, one through five scale.

Dr. Raul Pannala: I will just preface by saying that they're obviously, the Barrett’s experts and I do Barrett’s clinically and things like that. But I'm not sort of a Barrett’s expert in that sense of the word but based on the reading and based on my clinical experience, I think the molecular testing has come a long way. I think there's a lot of promising information. There is one randomized control trial going, showing benefits. So, at this point I would be in the two to three range. So, I'd probably pick two.

Dr. Angela: Great. And, do you have some thoughts about the data around the stratification of patients? And please do elaborate.

Dr. Raul Pannala: I think there's overall for identification of Barrett's. The data is much stronger in terms the differentiation between the low grade versus high grade dysplasia, at least that differentiation based on the available information. We probably need more data to sort of risk stratify to that degree.

Dr. Angela: Okay. So, if I understood correctly, there's some data for identification of dysplasia, excuse me, but in terms of the differentiation of low versus high grades, that's where some of the evidence is lacking. Did I understand that correctly?

Dr. Raul Pannala: Yes.

Dr. Angela: Okay. Dr. Wang, would you like to also respond please?

Dr. Kenneth Wang: Yeah sure. The difficulty has been that the molecular study have generally been used to prognosticate progression and not really for stratification for low versus say, high grade dysplasia. And you have to keep in mind, right? The only reason we have grades of dysplasia is to predict cancer risk. So I think in the sense that molecular testing can demonstrate possible progression to cancer, I think the evidence is pretty reasonable, but if you look at prospective clinical trials, not a whole lot of studies have been done to actually prospectively follow a group, a core patients, molecular testing that developed the lesion. Most of these are retrospective analysis. There's been a couple of these community based one from the Netherlands that looked at doing a molecular marker and following a group of non-dysplastic patients. And they definitely showed that there were genomic sets that corresponded with progression prospectively with a mean five year follow in that cohort.

And more recently there's been studies done with a prospectively follow cohort, but the molecular markers were assessed retrospectively and that's looking at copy number changes. And those studies were published in 2020, the earlier studies looking at copy number changes, date back to 2001. So, really, they've been around quite a while. So, I'd probably say there's reasonable data showing that molecular markers can be used to prognosticate. I probably give it as high as a four, but I won't say anything. I agree with Raul. There isn't much that that can differentiate low from high grade dysplasia because that a pathological diagnosis.

Dr. Angela: Okay. Thank you very much for your comments. Dr. Odze, can you also respond to this question?

Dr. Robert Odze: Sure. Yeah. I agree with mostly everything that was said so far. The question is a little bit difficult to interpret. So, I interpret it this way. We don't really have data, nor is there really much interest in data that subs stratifies high grade dysplasia patients into those who may or may not progress. So, I'm going to take high grade dysplasia out of the equation here. And the second thing is we're really focused on can we predict and separate patients with low grade dysplasia

to those who can and can't progress. And that's really where the big money is. We do know that there's a lot of low-grade dysplasia patients who don't progress over the course of many, many years. And there're others who do progress and progress fairly rapidly.

That's where the money is. Now in that specific category, I would agree that if there is some good mainly retrospective data or cross-sectional data, there is some prospective data that's emerging with P53 and with DNA content in that regard. So, I would say in that arena, I would probably put it as a two or a three. My problem with many of these studies though that have looked to stratify low grade displays and to progressors and non-progressors, is based on the outcome criteria that they use. Most of those studies are using either high grade dysplasia or cancer as an outcome. And generally, that's done because cancer and Barrett's is really not a common condition. And so, to develop cohorts based purely on evasive cancer, as an outcome is hard to do. And therefore, a lot of these studies combine both high grade dysplasia and cancer as an outcome. And I'm always uncomfortable with that.

Dr. Angela: Okay. Thank you for that. So, we have a clarifying question. Any questions for our medical directors?

Dr. Willner: Yeah. For the last speaker, this is Dr. Bien-Willner from Palmetto GBA. I'm assuming from your statement regarding the lack of need or desire to understand the value or for these biomarkers to distinguish high grade dysplasia is because high grade dysplasia patients are already very likely to progress. You didn't state that, but that was what I implied. Is that a correct assumption on my part?

Dr. Robert Odze: Is that a correct statement? For the most part, the answer to that is probably yes. However, we all do know from very nice and elegant work from Brian Reed's lab on following high grade dysplasia with the Seattle protocol, that there are indeed quite a few patients with high grade who don't progress over the course of many years. Again, part of the problem is how you define the outcome parameter. And I can tell you as a pathologist, that it is not easy, particularly on biopsy studies to differentiate high grade dysplasia from intramucosal cancer. And it certainly even more difficult to define invasive cancer because biopsies generally don't go beneath the Muscularis mucosae. So, it's hard data outcome criteria to evaluate. So, in short, I believe most high-grade dysplasia's if left untreated probably will progress, but there are definitely well-defined patients with high grade dysplasia who don't.

Dr. Willner: Can I follow up with another question? So, a lot of these services that we're looking at that have requested coverage or coverage policy are tests that are performed prior to any biopsy being obtained. So, a sample from the lower esophageal junction is obtained, and that will determine whether there is a likelihood of progression to cancer.

Dr. Stephen Meltzer: I can jump in there if you want.

Dr. Willlner: Well, just let me finish my thought and then yes, please, please, please address it. The idea that there are different kinds of dysplasia of consideration. You clearly have identified here that a distinction between the outcomes in high grade dysplasia and low-grade dysplasia. So is the relevance of the histological subtype, should that be a required consideration for these kinds of molecular studies?

Dr. Robert Odze: Steve, you want to go ahead and answer?

Dr. Stephen Meltzer: Yeah. So, am I allowed to? I sent the paperwork in, am I allowed to participate?

Dr. Willner: You are absolutely allowed to participate. It's a formality to get the conflict of interest forms, but I would also say if you guys believe you have a strong conflict of interest that may be relevant to the things you're discussing, you can go ahead and just also state what that is. It's okay if you have conflicts of interest, as long as they're understood, we don't have a problem.

Dr. Stephen Meltzer: So, I'm a co-founder of Capsulomics, which is a company that gets these samples. You were just referring to non-invasively with a sponge device, but we also have a prognostic product that works on paraffin biopsies of people with Barrett's. So definitely have a conflict of interest. So, is it okay for me to proceed?

Dr. Willner: Yes, of course. And I would also say the other speakers, knowing that can also comment on their behalf and their assessment of the data and your comments as well.

Dr. Stephen Meltzer: So, before I answer your specific follow up question, I just wanted to mention that there are these markers that are based on DNA. Several groups have done it, including my group, where you take an existing biopsy of a patient with Barrett's who has either no dysplasia, indefinite dysplasia, or low grade as was kind of alluded to, and try to predict their likelihood of progressing to high grade or intramucosal or invasive cancer.

So again, we have that endpoint question and we're using both VA studies, we're using both cancer and high grade as outcomes, but as Rob just mentioned, Brian did his elegant work. And Steven Sontag at the VA in Chicago also followed patient with high grade. And many of them don't progress as few as even 10% in some studies, which I think is low. It's probably at least 50% progress, but in any case, the endpoint was high grade because that's when the intervention occurs. That's when most patients today get intramucosal resection, or get endoscopic mucosal resection, or ablation with the microwave probe. These studies have not really addressed the difference between low grade and high grade. If I could ask this sample that you were talking about being obtained, was that obtained with a sponge or balloon device? Not endoscopy without biopsy?

Dr. Willner: Yeah. So, several of the providers who come to us seeking coverage for these kinds of services. Some of them have tests and procedures that would proceed any biopsy taking place. So, you wouldn't know in advance of some of these services what the grade of a tumor was.

Dr. Stephen Meltzer: Okay. So there, I have a little bit of a question, which is, the studies that I've seen with the balloon device as well as the sponge device have not given a progression risk. They've just told you whether you have Barrett's or not. So those studies just tell you, you have Barrett's esophagus, they're not very good at predicting progression or even diagnosing in the present moment, current cancer. So, the studies that I'm aware of, they're only diagnosing Barrett's metaplasia. Rob and Ken, you can correct me if I'm wrong.

Dr. Robert Odze: That's basically true. Some of them make an attempt to determine whether the Barrett's is actually dysplastic or high risk in that sense cross-sectionally, but it is true that the best of my knowledge, I have not seen a progression study based on those type of samples and tests.

Dr. Stephen Meltzer: So, I wasn't aware of that. I wasn't aware that they had requested that. That's interesting.

Dr. Kenneth Wang: I think, that's the non-invasive devices have primarily been for diagnosis of Barrett esophagus in Rebecca Cytosponge best three trial. That was really its purpose was to see the diagnostic rates of Barrett esophagus in the screen cohort versus the non-screen cohort. However, they also found that they diagnosed a fair amount of those patients. They found early stage cancers as opposed to the control group, which mainly were late stage. But once again, as Rob was pointing out, not many cancers developed, I mean, they only found in the screen total of nine patients, I believe, which I think four of them were cancers and five dysplastic Barrett's. And that's out of like whatever, close to 2,000 patients. So, it's not a large group, but those,

Dr. Stephen Meltzer: Yeah, they only found 160.

160 Barrett's, I think.

Dr. Kenneth Wang: Yeah. 160 total, most of which are non-dysplastic.

Dr. Stephen Meltzer: right.

Dr. Kenneth Wang: The nine were the ones with dysplasia or cancer.

Dr. Stephen Meltzer: Good point.

Dr. Megan Landsverk: This is Megan Landsverk with MolDX. So sort of what I'm hearing follow up with Gabe's question is that based on the original question that was posed about the data using to identify and risk stratify patients is sounds like you all feel that a

bit more confident in the early stages using these tests when they're differentiating Barrett, slow grades, but they're not really doing such a good job in getting enough samples to identify the high grade samples or the cancer, the individual or breast cancer.

Dr. Stephen Meltzer: I think that might be a little bit too harsh on these studies. In other words, they weren't trying to distinguish cancer from Barrett's. But they're probably identifying, well, they are definitely identifying both Barrett's and cancer. So in the Sandy mark with say in 2018, I think it was half of them had advanced Barrett's with high grade or cancer, so they can diagnose high grade and cancer, but they just don't distinguish between metaplasia and high grade.

Dr. Robert Odze: And they don't distinguish between high grades that progress and non-progress because the studies weren't designed like that.

Dr. Stephen Meltzer: Right.

Dr. Kenneth Wang: Even their markers, aren't really designed for that because triple factor three is more of intestinalized differentiation factor. If you actually had a highly undifferentiated cancer, would you expect the TFF three to be positive?

Dr. Stephen Meltzer: Right. And maybe even less likely.

Dr. Kenneth Wang: Yeah. They're not really, they're designed for the diagnosis of Barrett's, not really to pick up cancers per se. You're hoping that there's some Barrett's around the cancer.

Dr. Stephen Meltzer: That's right. Which of course sometimes gets obliterated, but that's usually, and the cancer gets more advanced.

Dr. Kenneth Wang: Yeah. That's usually the symptomatic patients, which won't be screening.

Dr. Stephen Meltzer: Right.

Dr. Angela: Great. Thank you all for your responses in the interest of time. I know we have a lot of additional questions here that we would like to get through. So, the second question is, does the existing evidence define a patient population that most benefit from the testing and have any of the studies included patients over 65 years of age? So, if you can see sort of a place where a patient might benefit from a non-invasive test, albeit we understand the limitations that you just outlined after the first question that would be helpful for this discussion as well. So, Dr. Pannala, why don't you take the first three to this one?

Dr. Raul Pannala: Sure. Now I think the answer to this is yes, in general because the traditional sort of the Barrett's archetype both for cost effectiveness, but also for studies has been the over 50 and typically males and typically Caucasian descent. The answer to have the studies included any patients over the age of 65 is yes. And I

think it's quite fair to take away that people over the age of 50 is the most studied group and would be the most likely to "benefit" based on the current evidence. So, I would give it a moderate sort of three to these questions.

Dr. Angela: Thank you. And when you say that they will benefit in what way specifically? I mean, being that the evidence is limited as we mentioned earlier, what exactly do you mean? Can you clarify?

Dr. Raul Panalla: I wanted to clarify also going back to the previous question that the panelists were also mentioned. I think the specificity of the question being asked in terms of, is the answer in terms of Barrett's in general, or are you asking very specific to the non-invasive tools? If you can clarify that. If it's in Barrett's in general, then there is a whole host of epidemiologic data showing that elderly, males over the age of 50, who are likely smokers, things like that, they're the most high risk to develop para esophagus and to progress. So, in that context, the answer to this is yes. The non-invasive marker studies that I have reviewed have included patients over the age of 50 and included patients over the age of 65 based on that epidemiologic data. So, that's what the basis of that is. If the separate question is how effective the tests are. That's a separate question, but if you have an effective test, the cost effectiveness modeling studies do show that they would be cost effective and beneficial in the about 50 age group. Does that answer your question?

Dr. Angela: Yes. Thank you. But just to clarify, we are looking at both for the non-invasive testing and how that would benefit such patients both as in terms of Barrett's identification, but also any kind of risk stratification that would impact further management of these patients.

Dr. Raul Panalla: Sure. I think to just sort of go back to the previous comments that were made, the risk stratification part between the grades of dysplasia is going to be challenging. But I think these tests and the studies were designed to identify Barrett's. This would sort of define a higher risk population. If you're just talking about age, that would be one sort of risk stratification Al beta general risk stratification parameter. But that would be the first sort of risk stratification parameter that I think would be used for the application of the test.

Dr. Angela: Sure. But that's independent of the findings of the test, right? That's an age stratification that the demographic variable in terms of finding the test in this population.

Dr. Kenneth Wang: Right. If you're asking the question, is would age be somehow specifically related to the application of these tests? At least my sense is that it would, it's being driven by the prevalence in this group. I don't think that age by itself would be somehow specifically related to molecular changes that would enable more identification. I think it would just be related to the underlying prevalence is the best I could get from that. But I'd be interested to see what...

Dr. Angela: Sure. No, no. we're looking at in these populations, how can we best serve these populations with their existing level of risk? So why don't we... Yes, go ahead.

Dr. Kenneth Wang: The only other point I was going to make, if you bring up risk, then obviously a non-invasive testing is a much less invasive procedure than an endoscopy. So, in that sense, that would be beneficial that way.

Dr. Stephen Meltzer: So, I can jump in on the age question.

Dr. Angela: Sure. Can you announce your name as before you respond, please? That would be very helpful as we move forward. So, we know who is speaking, then who to address next.

Dr. Stephen Meltzer: Steve, unless if Ken or Rob wanted to have an urgent comment, I don't want to interrupt. And I think I heard them chiming in.

Dr. Willner: Go ahead, Steve.

Dr. Stephen Meltzer: Is that okay?

Dr. Kenneth Wang: No, this is Ken Wang. I just say that, yes, they've tested these the best three studies, the population based cohort, which is the largest study that has been done using these non-invasive tests. The median age was 69 years old. So, over half the patients were clearly over 65. So, it's definitely been tested. But I took your question about defining a patient population that would most benefit would be those people most at risk for Barrett's. There's been a lot of literature on this subject using different models and they've been compared against each other. And the most recent study that I believe was published this year with Joe Rubinstein, looking at his score and the score from Adam Thrift and their group down in Houston, as well as two other different predictive models, all found that they worked pretty well to identify at-risk populations.

They're based on age as has been discussed by Raul earlier, gender, male sex, obviously, reflux history, history of hypertension. And I forget one other risk factor, but those are demographic factors. But using just those, oh yeah, history of smoking and alcohol usage, those demographic factors had an area under the curve of I believe of about 83% predictive value in a high-risk population. However, to my knowledge, none of the noninvasive tests used that to identify the population they were going to test. The best used individuals who were taking medications for reflux, which studies recently published have shown is probably not very predictive on its own to identify the population at risk.

Dr. Angela: So thinking that if we could clarify, are the studies inclusive of those high risk individuals that you mentioned? So above and beyond the age category with these other high-risk behavioral and other types of factors.

Dr. Stephen Meltzer: Yeah, my understanding is they're included, yeah. That people with those risk factors it's enriched for that population. This Steve, Steve Meltzer.

Dr. Kenneth Wang: They weren't enriched, Steve. They were the general practitioner practices. So it wasn't, they didn't select those out. The only-

Dr. Stephen Meltzer: Oh, oh, I...

Dr. Kenneth Wang: ... gratification, the only factor that led to them being invited to participate in the study was the use of antiacid medication. They did not discriminate. They did not select out men, for instance, they included both men and women. So, the populations were in there, but they were not enriched.

Dr. Stephen Meltzer.: So, I just wanted to come up with some clarifications cause we're using a lot of words that are a little bit ambiguous. So, we're talking about prediction and risk and progression. And I noticed the title of the Word document is for those that increase risk for progression to Barrett's esophagus. So, I think we need to really clarify these statements and questions, which risk are we talking about? Are we talking about people who were at risk of having or developing Barrett's metaplasia or are you talking about people who are at risk of progressing from Barrett's metaplasia to high greater cancer? I mean, those are really two different goals and questions, but meanwhile, I just wanted to mention that my own previous studies had found that age is so influential in the risk that we had to include it in our biomarker panel, both for our prognostic thing, which was back in 2009 on existing Barrett's patients and for our diagnostic panel, which was 2019 with a non-invasive device that balloons the sponge sampler.

So, age is extremely important in terms of risk, but there are other risk factors, of course. And then if you have a goal of benefiting population, so your second question is who would most benefit? I don't think you want to exclude people under 65. Yes, over 65 are the ones who have the highest risk of progressing to high grade, but Barrett's itself occurs way younger than 65. So, I'll shut up now.

Dr. Robert Odze: Yeah. And Rob here.

Dr. Angela: Thank you for your comments, Steve.

Dr. Robert Odze: I'm glad you made that. Hey, Rob Odze here. Steve, I'm glad you made that comment because I'm similarly confused. I was just assuming that we were talking about biomarkers in patients already have Barrett's, at least when we're talking about biomarkers. But as I read this question now, I'm not really quite clear on that.

Dr. Stephen Meltzer: Yeah. And most of the studies have not addressed that with the sponge or the balloon, they've addressed risk of having Barrett's metaplasia, correct?

Dr. Robert Odze: Correct. Yeah. And not exactly risk of whether you're going to "progress the Barrett's"

Dr. Stephen Meltzer: Most of the studies on progression, for example, by the comp Cernostics, forgetting the name of their molecular test. What was it again?

Dr. Kenneth Wang: TissueCypher.

Dr. Stephen Meltzer: TissueCypher, yeah. With the TissueCypher test and with our own study, which is a while ago, which is DNA methylation markers, they address people who have Barrett's that go to Rob Odds with their biopsy and Rob has their biopsy. He can send it to Cernostics, for methylation testing. That's a different question. If you have Barrett's and you know you have it, what's your risk of progressing to more advanced stages.

Dr. Kenneth Wang: To be honest-

Dr. Angela: So why don't, we take those two situations and identify the evidence for both of those. Cause it sounds like there's a little bit of additional evidence favoring, one of those circumstances versus the other, in terms of the other.

Dr. Stephen Meltzer: Wait. I don't follow you. So which evidence?

Dr. Megan Landsverk: This is Megan Landsverk, if I could interrupt real quick, I think the discussion that y'all are having right now, if we move to a couple of the next questions, we can actually skip down to question 1, 2, 3. I think it's the fourth question down. I think that question is sort of trying to get at some of the things you all are discussing right now in the evidence that's... Because there are two separate topics, right? There is risk stratification for development of Barrett's and then there's the more expanded risk stratification for development of the GI cancers. And I think we're trying to understand the whole spectrum end to end. So, I apologies on our side, if it was made too specific, but we're looking for evidence from both sides, is what we're going for. And if we want to skip down to question number four, and if you wanted to read that one, they could discuss that one a little bit.

Dr. Angela: At the end of the day, whether somebody has Barrett's or whether somebody is going to progress to cancer, we are trying to understand the landscape of these non-invasive tests for those people.

Dr. Stephen Meltzer: Okay. So, wait a minute. So only the non-invasive or what about existing endoscopic biopsy testing?

Dr. Angella: No, also with endoscopic samples as well. Also, with that. We're trying to understand the landscape.

Dr. Kenneth Wang: Just a clarification that the question here's the thing, the title that's written, just so you understand, no one's done studies that I'm aware of, that use biomarkers to identify patients at risk of progression to Barrett's alone.

Dr. Stephen Meltzer: That's right.

Dr. Kenneth Wang: Nobody does that.

Dr. Robert Odze: That's correct.

Dr. Kenneth Wang: To a very short cost, that's all you're interested in because nobody has used that to look at progression to Barrett's. And I think even, like myself, who's spent 30 years studying disease, I think I've seen it actually, something progressed to Barrett's, maybe once or twice in my entire career. So, it's not a very common occurrence that we can identify that.

Dr. Stephen Meltzer: Yeah. So, don't use the word progression in that sentence, only talk about progression of metaplasia to further stage.

Dr. Angella: Fair enough. And that's exactly the importance of this type of call. Please do continue to respond this is a very important clarification for us. So, go ahead. I won't disrupt your thought process here. So, we'll continue with number four, whoever hasn't addressed this, please continue.

Dr. Stephen Meltzer: I mean, I'm happy to jump in, but I've already talked too much.

Dr. Angella: We want to make sure to let you know that you're welcome to send written responses to these questions. And we would more than welcome that as well. We will have a transcript from this call, but we would really appreciate those written responses, as well.

Dr. Robert Odze: Well, it's Rob Odze here. I'll take a swing at number four here, as I understand it, and I'll broaden this to all procedures rather than just less invasive procedures, which I'm not quite sure how we're defining that specifically. But when you look at biomarker testing, that's been evaluated for the purpose of evaluating progression of patients who already have Barrett's. Most of the data comes from invasive tests that would be either biopsies or brush biopsies, such as WATS. Most of the data that's collected through, and Steve you would have to clarify this from me clearly, that comes from sponge or other devices is more of a cross-sectional sense. In other words, using those tests to define whether a patient has Barrett's esophagus or needs an endoscopy to confirm they have Barrett's esophagus or in some cases, whether they have perhaps more advanced Barrett's esophagus and even cancer, but again, cross-sectionally. And those collection devices have not been tested yet adequately for evaluation of progression of patients who already have Barrett's.

Dr. Stephen Meltzer: That's right. I agree.

I mean, the big difference is that the existing biopsies are much better for prognosticating known Barrett's. There are no real studies in the sponge or balloon device that are doing what the biopsy studies do, which is predicting progression.

Dr. Robert Odze: Right.

Dr. Megan Landsverk: So, in terms of these sponges and balloon devices and other such devices, where are they best indicated?

Dr. Stephen Meltzer: Just say, if you need an endoscopy, they tell you, "Well, you better have an endoscopy. You either have Barrett's or something worse." By the way, they're also tests for squamous cancer, but I guess we're not discussing that today.

Dr. Kenneth Wang: Well, you're not testing for squamous cancer with a EZO check though, or Esophagus, whatever you want to call it.

Dr. Stephen Meltzer: Yeah. So, Mayo clinic and, we have a paper in review, did the squamous cancer study where you actually are able to use these devices to detect squamous cancer, which is a totally different pathway than Barrett's and adenocarcinoma.

Dr. Angella: Go ahead.

Dr. Raul Panalla: It's Raul here. I was just going to make two points. One is, as it relates to the question six written on the document, going back to Dr. Odze's point about there is no data on surveillance and prognostication, so that partly also answers your question six, I think. And going back to your previous question of where there would be indicated from a purely epidemiologic perspective, it would be sort of an early screening test for people at higher risk for Barrett's is the way I think most of these are being positioned and the best pretrial was in that sort of population. So, I'd answer your question specifically.

Dr. Megan Landsverk: This is Dr. Megan Landsverk with MoIDx. I have a piggyback question on something Dr. Meltzer said about how he wants them to state these questions, I'd say answer the question, whether you need an endoscopy or not, that's question three that we sort of glossed over a little bit is what evidence is there available out there to indicate that those tests would preclude the need for things like endoscopies or biopsies? Can you all and talk about that one a little bit and then, how confident are you in the decision to use or not use that, that type of testing?

Dr. Kenneth Wang: Well, I mean, this is Ken Wang, like Steve said earlier, all the non-invasive tests are a guide to using endoscopy as the gold standard follow up. So, in order, I don't think anyone using the non-invasive tests intended them not to follow up with endoscopy, unless it's negative. If that's what you guys are asking, if you have a negative screening test, yes, most people would say that you wouldn't

need to follow through with endoscopy. If they're positive, they all need endoscopy.

Dr. Stephen Meltzer: Yeah. This is a really, this is Steve here, a really important question. So, we're talking about sensitivity versus specificity. So, with these tests, they generally are on the side of high specificity. I'm talking about the minimally invasive tests. They don't give you a lot of false positives. In other words, people who would unnecessarily have an endoscopy, they try to minimize that. And what they do is at the expense of insensitivity, that's the price they pay. Most of these studies, sensitivity tends to be a little bit lower. So false negatives are probably on the order of 10% or higher. This is exactly analogous to Cologuard, which has a disclaimer on there saying we only have 87% sensitivity, especially for large adenomas. So, it's exactly like Cologuard, which people are using. And how confident are you in a negative result? Well, not as confident as you are in a positive result and I'll shut up.

Dr. Willlner: I have a follow up question, it's Dr. Bien-Willner again. So you mentioned that there's a higher likelihood for false negatives and false positives by design, is there then a concern that you are going to potentially harm a patient that you would've otherwise gotten an endoscopy on, who you then don't get an endoscopy on because of a false negative.

Dr. Stephen Meltzer: Yeah, this is a chance for a lawsuit. So, you have to be heavy on the disclaimers. I know Lucid is already marketing their tests. So I don't know what their performance has been in the general population with the marketed, the commercial tests, I haven't seen any papers yet from Lucid. I mean, it would be very interesting to know what happened to the false negatives.

Dr. Willner: So, let me follow that up again. So as practicing experts in this space, if you perform a test and the screening test is negative, and you know that it has a high or relatively high false negative rate, does that mean you then are precluded from doing an endoscopy or would you still need to do an endoscopy to ensure that the patient isn't being misled by that potential for false negative results?

Dr. Stephen Meltzer: I want to let somebody else jump in?

Dr. Robert Odze: Well, it's Rob Odze here. I mean, if you're looking at a generalized screening tests, like some of these sponges, say the one from the UK, the goal here is to identify a patient population who needs to be endoscope in order to number one, confirm that they have a Barrett's esophagus based on the suspicion on the sponge. And two, is to make sure they don't already have a progressive lesion, a dysplastic or even cancerous lesion. So, you wouldn't be happy with a test that shows a high false negative rate because you'd obviously be suffering from a lot of missed virus and missed cancers. So, you want to adjust that fairly low.

So, for instance, on the UK test, which uses the Trefoil factor peptide; Trefoil factor is not a specific factor for Barrett's esophagus. It's a test that's used to identify a type of musin that is most often found in patients with Barrett's, but also found in patients with chronic gastritis, as well. So, when you find a positive test, you really need the endoscopy. Number one to show the patient has Barrett's and not necessarily a cardio or proximal gastric gastritis, and two, is find what stage that patient's Barrett's is in at that time.

Dr. Angella: Thank you. I'd like the others to also comment on the test performance characteristics and what evidence is available regarding the literature today for these tests that will help determine whether or not someone goes to endoscopy. Cause it sounds like you're not going to believe a negative result anyway, in many cases.

Dr. Stephen Meltzer: Okay. So, I want to jump in, just give me 30 seconds and then I'll let somebody else talk. If you look at the general sensitivity in the general at-risk population today, 17 million people with the risk factors mentioned above with GERD, et cetera, in those 17 million people, what is the current sensitivity? Zero. It's zero, because they're not getting endoscopy. We are not screening with endoscopy, not like colonoscopy, where 60% of the people who need it are getting it. The current sensitivity is zero. So, if your sensitivity with your test is 85%, you are rocketing from zero to 85%. So that's just a counterpoint to the point that I made earlier. And I'll let others speak.

Dr. Willner: If I could follow up with that statement, is the intended use of these tests where wherein there is suspicion of Barrett's esophagus and then the subsequent intent would be to do an endoscopy or is that not a correct statement?

Dr. Robert Odze: No, that is a correct statement.

Dr. Kenneth Wang: Yeah, if the test was positive, you follow up with an endoscopy.

Dr. Willner: But without the test in this clinical presentation, would you not also do an endoscopy?

Dr. Stephen Meltzer: Not everybody who has the risk is getting an endoscopy.

Dr. Kenneth Wang: Right now, unfortunately, the societies right now have not given good guidance on who to screen for Barrett's. They say certain people with risk factors should be screened, but they don't exactly tell you what kind of risk factors you need. Do you need one, do you need two? If you look at what ESO check is currently doing in their 1000 patient clinical trial, that'll be completed supposedly next year, they are using the presence of GERD and one of the other risk factors as the patient population they're to choosing to screen.

Dr. Willlner: So let me follow up, I understand that there's lack of clarity as to when it should be recommended, but if the understanding is that these tests would be used in

patients who would otherwise get endoscopy or being considered for endoscopies, it sounds like you're saying is that the real value to these services is to convince the patient that they should get an endoscopy.

Dr. Raul Pannala...: Let me jump in Raul here, I think I can clarify from a clinic perspective, I think that the role of these tests as it were, is the point that was made is most patients with who have Barrett's don't have some symptoms, they have risk factors like Dr. Wang was mentioning. But how many risk factors should buy you an endoscopy is unclear, but most patients with Barrett's don't have symptoms as it were. So, it's trying to identify these patients. So, they're not really presenting with any clinical features screaming, "I may have Barrett's!" Reflux is one and age and these things, but those are not necessarily indicative of underlying Barrett's. So, the main reason as I see it for these tests are to identify patients who may have Barrett's. And that's where the point was being made, it goes from zero to whatever number the sensitivity is. So maybe the question that is being asked is not addressing the clinical reality. The clinical reality is these tests are trying to create a newer non-invasive or less invasive method of screening for these patients.

Dr. Willner: So just to clarify, so I understand we're on the same page. If the creation of these tests is to maximize specificity, then these tests are not really identifying patients who have Barrett's, they're identifying patients who don't have Barrett's. So, then my question would then be, if that was the intent, why are these tests not created to maximize sensitivity and identify patients who would otherwise not get endoscopy without the result of this test?

Dr. Stephen Meltzer: You would have too many false positives and then you'll have $109 million or more, spent on and with the attendant risks, which are low, but there's still risks. That's the downside of that, if you maximize sensitivity.

Dr. Willner: Okay. So, that's understood. And so then let me follow up with one sort of last question on this thought process, which is, as we just discussed early on, the patients at greatest risk are going to be patients with, let's say high-grade dysplasia-

Dr. Stephen Meltzer: Okay. This is a different type of risk now. You're not talking about risk of Barrett's. You're talking about risk of progression.

Dr. Willner: Yes. Risk of cancer of a disease that has adverse effects on the patient's health.

Dr. Stephen Meltzer: Are you talking about risk at this current moment of having the cancer or high grade, or are you talking risk of getting it in the future?

Dr. Willner: At this time, at the time of the screening? So, so these tests are made to look for Barrett's, but the intent isn't only to identify Barrett's. It's Barrett’s or worse, correct?

Dr. Stephen Meltzer: Yeah. So here I have a little bit of a conflict of interest. So, I believe that some markers are better at that particular goal than others. So, I think the DNA markers, may they at least have the potential to identify high grade and cancer, but it hasn't been proven yet. Whereas the TFF3, probably not so much.

Dr. Willner: So just to put this all together and hopefully you see the train of thought. If the test are designed to have high specificity to prevent unnecessary false positives, and then the concern is a false negative, would there be additional concern from you all, if these tests didn't adequately or couldn't adequately detect cancer or high grade dysplasia or the most, let's say, advanced disease or is that an irrelevant thought?

Dr. Stephen Meltzer: Oh, of course it's relevant. Yes.

Dr. Kenneth Wang: It's extremely relevant. But currently the best method, really the only specific method, of identifying high grade disease, high grade dysplasia, or cancer is endoscopy with some sort of tissue acquisition device, whether that's by brush or by biopsy. The goal is to identify a patient group or a population group who are at risk to have that at the moment. And that's the purpose of the screening protocol. There is no test, as far as I'm aware of, that adequately can be done and combined both a screening system with identification of a patient who already has a high-grade lesion.

Dr. Willner: Does that cause for concern for initiating a screening test for a patient who may be walking in the door, who you're trying to evaluate for disease, if that screening test is not capable or hasn't demonstrated to be able to identify high-grade.

Dr. Stephen Meltzer: No. I think the answer is no because these are people who would not get any testing at all. And so, the benefit... population is to identify Barrett's. It's icing on the cake if you can distinguish Barrett's from high grade, but once you have Barrett's, you go to the next... It's a reflex test. You go to the endoscopy.

Dr. Willner: Okay. I think we can move on. But I think the general thought that I would like to have others comment on is the concern that, and I can't get this one out of my mind, which is, if the general population at large who is available or should be getting a endoscopy is not getting them for whatever reason, gets a negative test result and some of that population has high grade disease, what is the risk that's posed to the population for those specific individuals who may be then persuaded to not get an endoscopy? Is this a fair evaluation of the data or is this irrelevant in light of the general population and the characteristics of that population that that becomes a drop in the bucket to those that were…

Dr. Stephen Meltzer: Well, all of those patients, presumably they don't have dysphagia, are being missed. They're all being missed. So, 95% of the cancers are people who've never been screened, never had endoscopy, the adenocarcinomas. So, if you look at the population as a whole, yes, false negative is a lawsuit, potential

lawsuit, but most of these patients are going to get cancer anyway with the current practice.

Dr. Megan Landsverk: My understanding that they're also, this particular population, if they just say have GERD plus an additional factor, those individuals are not getting an endoscopy anyway.

Dr. Stephen Meltzer: Not consistently.

Dr. Megan Landsverk: Correct. And so, either they're not going to get one and they would get missed, or alternatively they have this test and they become a small fraction of individuals that get the test and have a false negative. The path forward for that individual really hasn't changed because they were not likely to get an endoscopy in the first place. That's sort of what I'm hearing.

Dr. Stephen Meltzer: That's right.

Dr. Megan Landsverk: Is that correct?

Dr. Stephen Meltzer: Yes. I agree.

Dr. Kenneth Wang: That's correct because... This is Ken Wang. There is no consistent guideline. When you say they should have gotten endoscopy, there is no societal guideline that consistently recommends endoscopy for these patients. That's part of the problem right now. It's not like screening is being touted and it's not being done. It's not being recommended by most societies and where it is being recommended, the recommendations are very vague. So that's part of the problem right now. It's not like their... have advocated Barrett's screening program.

Dr. Angela: Okay, go ahead, Megan, did you have another question?

Dr. Megan Landsverk.: No, I was just saying thank you. This has all been very informative.

Dr. Stephen Meltzer: I have a meeting in 10 minutes.

Dr. Kenneth Wang: These non-invasive tests are the first time that somebody has recommended a screening program, systematic screening program for a Barrett's esophagus. So, to compare it to endoscopy, I think is a little unfair because it's not a current practice that some guy comes in and you immediately say, "Hey, let's screen you." It's done but it's very inconsistent. These devices are the first time it's actually being tried.

Dr. Stephen Meltzer: Right.

Dr. Angela: Okay. So, in this case it seems like we're talking about screening which is a topic for discussion in these asymptomatic patients. However, I do want to just take a

moment to make sure that the callers that are not speaking, the non-panel participants, are also welcome to submit responses to these questions as well and to provide your comments. So please do that. Those are all welcome. Let's move on and discuss.... Let's take this next question in order and I'm sure we'll keep circling back. But what evidence has been published to indicate a reasonable success rate of swallowing for a non-endoscopic device used for molecular biomarker testing?

Dr. Raul Pannala.: It's Rahul Pannala here. I can go first based on previous. So based on the studies, it seems to be about 90%. So, I think the evidence is quite good. All the capsule-based studies that I saw were about 90%. There is one device that has to be inflated, but even there, I think the swallow rate is 90% or more.

Dr. Angela: Thank you. Our other panelists?

Dr. Stephen Meltzer: Yeah, some of them claim even higher rates. Go ahead, Ken.

Dr. Kenneth Wang: I'm sorry. Is that question just about whether or not once they arrive at the physician's office or screening office, can they swallow? I think a bigger question is how many of them actually will go in for such a test. In other words, if you tell them they need to swallow this device in order to be screened, how many will actually go for the screening?

Dr. Stephen Meltzer: Yeah. So, the best three was they divided 6,000 or 7,000 were asked to swallow and another 6,000 were not, that was a control group, and of the 6 or 7,000. I think it was 2,000 that agreed to swallow. Is that right, Ken?

Dr. Kenneth Wang: Yeah. That's about right. It's only a 30% rate of those. Of course, the point was that these people are only invited with a letter. There was no pressure or anything like that to participate. But that's a very important...

Dr. Stephen Meltzer: Absolutely.

Dr. Kenneth Wang: ... to this swallowing business, because once you're told that you have to swallow this, less than a third of the patients actually will consent to that, will come in for that.

Dr. Stephen Meltzer: I'm doing a study currently. I've gotten 600 sponges over the past several years, but it's probably like Ken said, I've asked a lot more than that and they just said no, even when I ask, and then when one of my coordinators ask it's probably even lower.

Dr. Angela: Okay. Thank you. Thank you for that. It sounds like there's a consensus on that one. Of course, it sounds like these are also patients that aren't necessarily given the option of do this or get an endoscopy per se, correct?

Dr. Kenneth Wang: Yeah, this is a screening test so it's just, "Will you participate?"

Dr. Angela: Right. Which is a different patient population certainly. Okay. Let's move on then.

Dr. Kenneth Wang: Oh, no, it's not a different patient population. It's the same for screening.

Dr. Stephen Meltzer: Right.

Dr. Kenneth Wang: It would be the same kind of population.

Dr. Stephen Meltzer: Agree.

Dr. Angela: So are these patients willing to undergo endoscopy, these same 30%?

Dr. Stephen Meltzer: Well, they're not all getting offered endoscopy.

Dr. Kenneth Wang: Well, we actually did a study where we looked at trans nasal versus standard endoscopy and actually trans nasal is a different type, it's not a capsule, but actually for standard endoscopy, the acceptance rates is actually a little bit higher because we offer sedation. Patients are sedated for the procedure. Whereas these capsules are all unsedated, they're all awake for it.

Dr. Stephen Meltzer: That's right. I mean, it's not massively painful, but it's not exactly fun to swallow one of these things and have it pulled out. It's not something that you really want to do. It's not totally pleasant.

Dr. Kenneth Wang: Yeah. The advantage of endoscopy isn't that it's any nicer, it's just that you're not aware of it because you're not fully conscious.

Dr. Stephen Meltzer: You don't feel a thing.

Dr. Kenneth Wang: Yeah. So that's something to consider.

Dr. Angela: Thank you. And to clarify, because I know we keep using the term screening, but this is in essence in high-risk patients, this isn't just a screening tool in any patient, is that correct?

Dr. Stephen Mel...: Well, that's a really big question. So, in other words, eventually we would like it to be like Cologuard, those of us who advocate these approaches, where everybody gets screened. But right now, it's very hard to justify so it's mostly being studied in high risk population.

Dr. Kenneth Wang: Yeah. But high risk is relative. I mean, I wouldn't call them very high risk. It's not like if you said to them, "I won't take a sponge, you must have an endoscopy," that's not the case.

Dr. Stephen Mel...: Right.

Dr. Angela: So that line is- Go ahead.

Dr. Stephen Meltzer: As Dr. Pannala alluded to, a lot of people with BE seemed to develop a protection against symptoms. Not all but certainly a huge percentage. So, when you say high risk, it usually includes GERD symptoms. Some of these people don't have any GERD symptoms.

Dr. Angela: Sure. It sounds like there's a real issue with guidelines support, but also with understanding who would be best served by such tests. Right? Because there are numerous risk factors, some are more common than others. But in a patient with multiple risk factors, it seems like the tide would move closer to endoscopy and then in the lower-risk patient, it's nevertheless, some of these risk factors is unclear. Is that a correct statement as to how you would proceed?

Dr. Kenneth Wang: Yeah. Except there's been a lot of work done on these risk factors. They've actually weighted them. There are models made of them. There's like four or five of them that have been tested in multiple cohorts. They're predictive value now of weighted risk scores is well over 70% with the best one being 83%. So, they already have tools how they can identify that high-risk group. And actually, what you guys should be thinking about is that's a whole lot cheaper than using a sponge, but that's just for screening.

Dr. Stephen Meltzer: Yeah. And a patient doesn't have to agree to a procedure at all.

Dr. Kenneth Wang: No, that could be identified... That's how come everybody's using demographic factors that they can get right off a patient chart rather than having even an interview. But it's something to consider. I think what hopefully we evolve to, I think what Steve would like to do, is to be able to use these tests as the first step before endoscopy in those patients.

Dr. Stephen Meltzer: Right.

Dr. Angela: Sure. And then we'd have to understand the data surrounding the utility relative to when the data would support the endoscopy or the lack thereof following this kind of test because we've talked about the test performance characteristics and it sounds like there's still a lot of unanswered questions there with a high enough false negative, which is what-

Dr. Stephen Meltzer: I would put a caveat about restricting the noninvasive test to the less at risk people, is that most of the people who are at the highest risk are still not getting scoped, because they present to their primary care doc and he gives them a proton pump inhibitor and then they get better. So, they never proceed to a gastroenterologist. They don't get endoscopy.

Dr. Megan Landsverk: So, these tests would almost be for lack of a better word, almost like an additional risk factor that one would put into the whole gestalt. So you have an individual that has a history of GERD or a family history of Barrett's and they

come in and they're obese and they're a smoker and they're a white male over 50 and so he's checking all of the boxes, would one go straight to an endoscopy at that point or would this test kind of help even further stratify whether or not that individual should have an endoscopy?

Dr. Kenneth Wang: That study hasn't been done.

Dr. Stephen Meltzer: We don't know that.

Dr. Kenneth Wang: The screening populations that's been selected for these devices, haven't utilized all those risk factors. They've used some, but they haven't used a highly predictive model to bring up a highly enriched population.

Dr. Stephen Meltzer: Yeah, that's true.

Dr. Angela: Thank you. And why don't we then continue, and we'll jump quickly to question 10, because this is kind of what we keep talking about. And then we can go backwards.

Dr. Stephen Meltzer.: I'm going to have to leave shortly. I'm just letting you know.

Dr. Angela: Sure, sure. Thank you. So, we'll let you take the first answer to question 10, which is, is there evidence to finding the clinical setting in which a non-invasive biomarker, I'll say, could be performed? So again, we've been talking about it, we've been talking about the data or lack thereof. We've been talking about test performance characteristics with some of these tests. When and how would one use this today with the current evidence that exists?

Dr. Stephen Meltzer: Okay. So now we're talking about the sponges and balloons. Well, we call it minimally invasive rather than non-invasive because you do have to swallow this thing and it could potentially get stuck in your intestine. So, it's not noninvasive, but it's minimally invasive. You were just alluding to it. I think, for now, people with those risk factors that were just mentioned in the primary care setting, and that's the key point here, in the setting in which endoscopy is not... They're not seeing a gastroenterologist. If a gastroenterologist saw somebody with all those risk factors, they'd probably recommend scoping if they've never been scoped. But if a primary care person saw them, they'd probably just give them a proton pump inhibitor. So, we're trying to convince the primary care people, and this is a tough sell, to do the screening in their office.

Dr. Angela: I see, so this would then proceed, in essence, the referral to the gastroenterologist in somebody with few risk factors as opposed to somebody with all of the risk factors.

Dr. Stephen Meltzer: Yeah, probably GERD plus one, like you said, GERD plus one.

Dr. Angela: Right. Right. Understood.

Dr. Stephen Meltzer: And I'll leave it to the other people to talk.

Dr. Robert Odze: Rob Odze here, and then bearing in mind, that's been said here many times, is that many Barrett's patients don't have any symptoms. So, based on that GERD symptoms plus one, you're still going to miss many patients.

Dr. Stephen Meltzer: Oh yeah. So that reminds me Rob, that's a really good point. So, people come in and the primary care doc says, "Hey, you need a colonoscopy. You're 50." Well how about every time you get a colonoscopy, just have them flip you around and do an endoscopy? That's another clinical setting where I think... Well, of course, now we're talking about endoscopy. Yeah. But if you can flip them around and do an endoscopy, you can definitely do a sponge in anybody who's being screened for colon cancer.

Dr. Angela: But the key, it sounds like, is that the data is lacking in those patients, the GERD plus one patient, who would use this, what outcomes there are surrounding the use of this type of test in that setting, it sounds like those studies are still yet to be done.

Dr. Stephen Meltzer: So, the best three study was essentially that, although they didn't ask for GERD symptoms. That was their general population screening.

Dr. Kenneth Wang: Yeah, they used anti acid medication as the surrogate.

Dr. Stephen Meltzer: Right.

Dr. Kenneth Wang: So, all those patients were taking, being prescribed anti acid medication. So, in essence, that is the best data on a clinical setting in which the non-invasive test has been done. And those patients all were on... Supposedly had dyspepsia or reflux type symptoms.

Dr. Robert Odze: And let's face it, Rob Odze here, I'm curious to hear what others on the phone would think as well. But if we're really going to make a dent in this and really reverse the current 95% of counting that are not known and reverse that to the 5%, we really need a general population screening device because otherwise we may make a dent in it but we're not going to get anywhere close to 95% that we need.

Dr. Stephen Meltzer: Yeah, I agree.

Dr. Kenneth Wang: Yeah. I think I agree with Rob's sentiment, but I think the key is I think to use the device, screening device, in a more enriched population than to do the entire general population.

Dr. Stephen Meltzer: Yeah. We can't jump to that right away.

Dr. Kenneth Wang: Because I think if you really say you're going to use a sponge in the entire United States population, non-selectively, that's not going to work. And you're going to have to tone it down.

Dr. Robert Odze: Around patients who are 50 and over getting a colonoscopy idea. That makes a lot of sense to me.

Dr. Kenneth Wang: Yeah. But then you can refine it further. Like I say, if you look at Aaron Thrift's model or Ireland's model out of the Baylor Group, they're already 80 plus percent predictive with their risk factors, all of which can be captured from the patient medical record.

Dr. Raul Pannala: Yeah. Rahul Pannala here, I was going to substantiate, I think the model that is going to eventually... is an enrichment model based on these data parameters and cost effectiveness studies. I think one from about GERD versus non-GERD based cost effectiveness. So, when you put the other parameters into the model, it is cost effective even in a non-reflux space enrichment model. So it seems like it's going to go that way in terms of pretest enrichment followed by a noninvasive test is where...

Dr. Stephen Meltzer: All right. I got to take off guys. I'm so sorry.

Dr. Kenneth Wang: See you Steve.

Dr. Stephen Meltzer: Okay. Thanks a lot.

Dr. Angela: Thank you for your time.

Dr. Kenneth Wang: Yeah. I mean, all the models are designed so that no single factor would preclude you from getting screens such as not having GERD or even being female rather than a male, but you have to have other risk factors.

Dr. Angela: Okay. Thank you. So, it seems like there's consensus on the clinical setting question about when this essay could be used. Is there anything that we still have to address regarding this? Because again, if somebody has a low risk versus a high risk, I think that was the initial thought of the differentiation and then who's going to progress in that setting. And we've kind of turned our focus a little bit to more of patients with some risk factors who should be referred or who should be getting an endoscopy that are not in fact, and maybe this is the more clinically useful situation for these more minimally invasive tests. Is that a correct statement?

Dr. Kenneth Wang: Yeah. I mean, I think so. Yeah, I think that's essentially what we're saying.

Dr. Robert Odze: Yeah, I would agree with that.

Dr. Raul Pannala: Agree.

Dr. Angela: Okay. Thank you very much. Okay. So, we had jumped to question 10. Why don't we go back to six, which again is a little bit based on how the initial focus was for this conversation. So, basically question six states, what outcomes are there in the literature indicating how to follow a patient with Barrett's with molecular testing instead of endoscopy? So is that a fair question with "instead of" but I'll let you respond. Let's start with Dr. Pannala and then we'll just continue.

Dr. Raul Pannala: Oh, I think this has been addressed before. I did not see any data on surveillance. And I think for the intent of the non-invasive tests is to quote unquote detect Barrett's. And I don't think there's any performance data in surveillance.

Dr. Robert Odze: Rob Odze here. There are currently no molecular tests that could be used in lieu of endoscopy to predict which patients with Barrett's will progress or which patients with risk factors will have Barrett's esophagus.

Dr. Angela: Great. Thank you. It's easy when there's consensus, right? So, in this case it sounds like there isn't, there's too much else to discuss. So, we phrased the question as "instead of" endoscopy, should we address the question of, in addition to endoscopy? Can we talk about outcomes data in that setting?

Dr. Robert Odze: What do you mean specifically by outcomes data? You mean progression of Barrett's to cancer?

Dr. Angela: Sure.

Dr. Robert Odze: Well, if you're looking at progressions of Barrett's to cancer, then all effective devices, if you will, or biomarker tests for the most part are based on tissue acquisition and that would mean endoscopy.

Dr. Angela: Great. Thank you.

Dr. Robert Odze: So, they'd be done on top of the endoscopy on the specimens that are derived from endoscopy. I mean, there are some serologic markers being developed for detection of cancer in general and sometimes of the upper GI tract, but I don't think they're at the point yet where they're useful on the scenario that you're depicting, which is a known patient with Barrett's who you're trying to predict whether they will or won't progress to cancer.

Dr. Kenneth Wang: Yeah. And just a clarification, this is Ken Wayne again, molecular testing in addition to endoscopy currently is only recommended by the British Society of Gastroenterology and that's only immunohistochemistry for p53.

Dr. Robert Odze: That's correct.

Dr. Kenneth Wang: And most of the time that's used just to sort out high-risk patients with equivocal dysplasia or low-grade dysplasia. There isn't really any recommendation on using molecular testing with endoscopy other than that.

Dr. Angela: Great. Thank you. Thank you for that. Why don't we move on then to question seven. For the outcomes that we have discussed, how frequently would such a test be needed to be repeated to ensure confidence that the patient has not developed disease needing further investigations? So, we talked about our concern with some of these performance characteristics. How frequently would you expect in the clinical settings where you would use such a test where we'd have to repeat this, let's say in a negative case?

Dr. Robert Odze: And what tests are you referring to, molecular biomarker tests in patients with known Barrett's?

Dr. Angela: We could talk about that and we could talk about these minimally invasive biomarker tests that we discussed as well for identification.

Dr. Robert Odze: Oh. And those minimally invasive tests, as we mentioned, that's purely for the purpose of screening to get that patient into the system. So, their endoscope for confirmation of the diagnosis and evaluation of their current risk. At that point, then we're talking about endoscopy with tissue acquisition and biomarkers that are applied to that tissue for future risk assessment. And I don't think anybody knows yet, nor have those studies been done on how frequently those would need to be done in patients who would come up with a negative test in that regard.

You get your endoscopy, you get your tissue, you get your biomarker test, whichever you choose to do, and if that biomarker test comes up as low risk, there isn't great data yet. There's some emerging to define time intervals of which you would need yet another. And part of the problem there is because we haven't been able to do those tests on long term outcome patients, say greater than five greater than 10, even greater than 20 years.

Dr. Angela: Yeah. It sounds like the data is somewhat questionable for the single time point and of course at this point, we're talking about repetition and then longitudinal data, which just does not exist. So we do understand that and appreciate that. Thank you.

Dr. Megan Landsverk: This is Megan. I've got sort of a follow up question for that. Say if this is to be used to take those individuals that have GERD and multiple risk factors and screen them for whether or not they've developed Barrett’s, or some non-dysplasia again, those individuals would not be getting endoscopies on a regular basis, correct? Those are just the individuals that are monitored by your local doc. And they're not getting sent to endoscopy. They have to have additional factors that would make one suspicious enough to send them off to GI to get an endoscopy. Am I understanding this all correctly?

Dr. Robert Odze: Ken, do you want to address that? Otherwise, I will.

Dr. Kenneth Wang: Well, I think I usually that's true. They usually have to have multiple risk factors to warrant endoscopy. I think the question as written, I'll interpret it as if you did a noninvasive test and it was negative for Barrett's, how often would you need to repeat it to ensure that there isn't Barrett's there, as has already been stated. There hasn't been a study that I'm aware of that they have repeated the non-invasive test to see what the yield would be.

Dr. Angela: Great. So in a patient with GERD, we've gotten one risk factor of the many that have been discussed already. What is the value, clinically, for molecular tests?

Dr. Kenneth Wang: A molecular test to exclude Barrett's?

Dr. Angela: Correct.

Dr. Kenneth Wang: Yeah. In a patient with GERD, like has been stated several times, GERD by itself is not a great marker for Barrett's esophagus. And there has not been a study that I'm aware of that says that a molecular test is of much value in discerning whether or not they have Barrett's esophagus. Outside of the BEST3 trial, which you can call that a molecular test. There isn't a lot of value in just plain GERD.

Dr. Angela: Okay. It sounds like the value is really... We've talked about the minimally invasive test, but in the GERD plus one, so a molecular test is a GERD plus one situation. Would there be any other validity other than what we've discussed?

Dr. Robert Odze: Again, when you say molecular tests, are you talking about a sponge device or a capsule device that utilizes molecular methodology to determine if a patient has Barrett's at that time? Or are you talking about a molecular test that is done on an endoscopically acquired tissue sample? Because when you keep on saying molecular tests, I think what you're really referring to is endoscopy plus tissue acquisition plus a molecular test.

Dr. Angela: I think we're looking at both scenarios, but we're also looking at primarily the first where it's the non-endoscopically obtained, biomarker-

Dr. Robert Odze: Minimally Invasive biomarker

Dr. Angela: ... Or molecular information.

Dr. Robert Odze.: So I think I can make that fairly simple and concise in that currently, any sponge device or capsule device or minimally invasive device that is used out there, is using whatever formula they are, whether that be immunohistochemistry or in some cases molecular, to determine whether the patient has Barrett's esophagus or in some cases, cancer at that time. They're not being used for risk assessment once the patient is determined to have Barrett's esophagus. And

the determination for Barrett's esophagus is ultimately still done by confirmation with an endoscope.

Dr. Angela: Thank you. Any other thoughts on this question before we proceed? We're getting close to the end here. And we still do have some time. We've done well on our time. Would any of our other panelists like to comment?

Dr. Megan Landsverk: This is Meghan with MolDx again, and I just want to make sure that... What I'm hearing from everybody is that there really are... The questions have sort of glommed everything together, but there are essentially two separate scenarios that we're kind of smooshing together, unfortunately, here. And the one is the individuals that may have a predisposition for Barrett's, and we're using the one set of tests, is to get the minimally invasive tests to determine whether or not those individuals either have Barrett's or some sort of non-dysplasia.

And we're developing towards that versus those individuals that have already been identified at a higher risk and have had an endoscopy already. And that the tissue that has been obtained from endoscopy is being tested molecularly for doing further assessments or something like that. So that's sort of what I'm hearing that there's two separate use case scenarios for 'molecular testing' in this environment.

Dr. Kenneth Wang: Yeah. One is for diagnosis, diagnostic validity of Barrett's esophagus, and the other is for prognostication. Once we know they have Barrett's, using tissue acquisition to determine their prognosis, whether or not they're going to develop cancer.

So, there's a diagnostic and a prognostic use of molecular testing.

Dr. Angela: Sure. And we've addressed the diagnostic. And in terms of the prognostic, do you have comments about that?

Dr. Kenneth Wang: I think we addressed that at the beginning. This is Ken Wang. There's a number of studies out demonstrating that various markers, copy number abnormalities, mutational analysis, that kind of molecular marker is predictive of cancer development. But none of them have actually been accepted by societies this time with the exception of p53, even a histochemistry.

Dr. Angela: Right. So, the list is emerging, but not accepted. Thank you for clarifying that. I know you did say only by the British or there are some guidelines related to the use of these molecular test for prognosis. Is that right?

Dr. Kenneth Wang: That's correct.

Dr. Angela: Okay. Thank you. All right. We're kind of jumping back to question nine, if a clinically validated biomarker test were available, what additional barriers do we have to its use? I know we talked about the clinical setting quite a bit, but what

barriers do we have for implementation of such a test? Assuming the test performance characteristics are what we would like to see.

Dr. Raul Pannala: I can get started here. Rahul Pannala. I think the data would suggest, and this is alluded to before, is the acceptance rate is in the 30% range. The patient acceptance is, I think, going to be a big barrier. That's the first thing that comes to mind, assuming that all the performance characteristics fall into play and we are not debating the false, false positives and false negatives.

The other thing is obviously the clinical setting. This is a new paradigm because we are asking primary care physicians potentially to do this. So, this would be a new thing, but they do a lot of other screening tests. Potentially that's surmountable, but it would be a new thing for them. And then obviously the third thing is, which patients should we use it on and identifying that enriched population. Those are the three things that come to my mind.

Dr. Kenneth Wang: This is Ken Wang. Just to clarify, are you talking about a biomarker test for a non-invasive test, as you were talking about earlier, the sponges and the EsophaCap and EsoCheck, those kinds of devices with a validated biomarker, or are you talking about a biomarker that we get with endoscopy and tissue acquisition?

Dr. Angela: The former. A biomarker from these minimally invasive tests.

Dr. Kenneth Wang: Yeah. I think Rahul touched on all of the things they identified in the BEST3 trial. I would bring up a fourth, which is that even though the BEST3 demonstrated a much higher rate of detection of Barrett's esophagus in the screened population, there actually has been requested a BEST4 study because according to NCI guidelines regarding cancer screening, the phase five is actually demonstrating cancer control. The tests have not shown... They've identified Barrett’s, but they haven't actually shown that you can decrease the number of cancers or increased the prognosis of the screen population. That's what the best group, Elizabeth Fitzgerald group, is currently doing is ramping up for a cancer control study. And that data is lacking for the noninvasive test.

Dr. Robert Odze: Yeah. That's a good point, Ken.

Dr. Raul Pannala: Yeah. It's like a lead time bias kind of a thing.

Dr. Angela: Thank you. And for the other situation, then barriers for molecular testing on endoscopically obtained tissue specimens. We talked about IHT for p53, but we talked about some of these other molecular tests that the British societies have adopted that have not been adopted here. What are barriers that you see to those here in the United States?

Dr. Robert Odze: Rob. I would say well, there are a few that are worthy of comment and that is, some relate to the economy, economic aspects, the cost of the procedures, the

delay in time of the procedures, the technicality of the procedure and where these can be done. Some of them like deep sequencing can't just be done by anybody, the diagnostic reproducibility of procedures, such as p53 immunostaining. There is yet to be... When good predictive biomarkers do become available and then enter the guideline's standardization and figuring out the logistics will be another aspect of this that needs to be worked out.

Dr. Angela: And do we have outcomes information from the British societies that have adopted some of these tests that we can look to?

Dr. Kenneth Wang: No, they based the recommendation on... Didn't really carry it through to hard outcomes and have not been done in large prospective cohorts. No, we don't have that information.

Dr. Robert Odze: Right. And as Ken said, as best as I'm aware, I think, even though p53 is endorsed or accepted in the UK guidelines, it's primarily, if not exclusively, for diagnostic purposes and not for prognostic purposes, but I may be wrong on that.

Dr. Kenneth Wang: They recommend it, but you're right. Most of the time it's for the indefinite, for dysplasia to kind of throw them into the law grade group or not. You're absolutely right on that. They don't usually use it like in a high-grade dysplasia.

Dr. Angela: Gotcha. This is actually referring to question eight. We kind of jumped to it in terms of the utility and outcomes associated with some of these molecular tests. And do we have information about how some of these, whether it's Barrett's or high-grade dysplasia, how these may be missed by molecular testing? It sounds like we don't have that level of granularity yet. Is that correct?

Dr. Robert Odze: Yeah. And I think question eight refers specifically to screening because in the situation where you have a known Barrett's patient, and whether they do or don't have low grade dysplasia, the purpose there is for prognostication, not for something missing. Clearly, we do miss a lot of dysplasia's and cancers with the routine Seattle forceps biopsy protocol. And clearly, I think there's good data to suggest that brushing techniques that acquire more surface area decrease these false negatives in that regard.

But I think what you're saying is that we don't really have a molecular... When you're talking about a molecular testing missing a cancer, I think for the most part you're talking about, is there a molecular test that is used to diagnose a cancer at this moment? And also, some of the sponge devices do have the capability of determining whether a patient with Barrett's has more advanced disease. I'm not aware of any studies that have done this specifically related to question eight.

Dr. Angela: Thank you. Would others like to comment on that question before we move on where we're getting to our end here?

Dr. Kenneth Wang: I would agree if you're talking about the non-invasive test missing a malignancy, most of the trials, depending on the device you're talking about, haven't moved beyond a cohort studies, deeply enriched cohort studies with some patients with Barrett, some without, and then testing both groups. And these are all known groups. To get to this question, the only one that would have a chance at that would be the British study, the BEST3 study. And they really had very few cancers overall.

Dr. Raul Pannala: Yeah, a handful.

Dr. Kenneth Wang: That they can't answer that. How many did they miss? They only found four. It's treatment groups. There's no way they have a power to determine what the actual miss rate is of a malignancy.

Dr. Raul Pannala: Yeah. Here, the only other sort of thing that I would add is the context. This also has to be interpreted in the context that while endoscopy is the gold standard, it's not perfect. And a lot of, I think 25%, if not mistaken of cancers are diagnosed within a year or a year after endoscopy. Especially for early cancers. Going back to Dr. Wang's comment about finding the true miss rate it's a much harder question than...

Dr. Angela: Sure. Thank you. Thank you all. We actually have addressed all of the questions that were written in advance. Are there other things that you would like to address related to this topic that perhaps we haven't specifically asked?

Dr. Robert Odze: No, I guess the only thing I would mention is... Rob Odze here... is that we've talked a lot about screening devices and the application of molecular diagnostics in that regard and a little bit about molecular diagnostics for prognostication, but bear in mind as of today, there are no accepted molecular biomarker tests that are used in guidelines to prognosticate. We still use the old system of taking four quadrant biopsies every once two centimeters, and we all know that that is a doomed system because of the high miss rates that are associated with that protocol. And that's really an area that needs to be improved on because we all do that. We all accept it, but we all know it's quite a flawed system.

Dr. Kenneth Wang: Yeah. I agree with that. This is Ken Wang, Rob. And I'd add one more comment to all this. That it has a lot to do with the topics today. And that's to consider NCI has a lot of thoughts about this and that's the problem of length time bias. And that has to do with the fact that slower progressing cancers, even those that may not cause harm to the patient, are much more likely to be discovered by screening tests than rapidly progressive cancers that kill patients.

And just to point that out in the BEST3 trial, virtually all of the cancers found in the screening group were early stage cancers, whereas those in the usual care group, the control group, tended to be advanced cancers that were most likely fatal. That may reflect the fact that patients who are willing to be screened, are unlikely...

The kind of cancer is going to cause them harm or kill them. We don't know that, like I said earlier. There just wasn't enough cancers, in either group, that you can draw firm conclusions. But certainly when you look at the stages of cancers in both groups, it seems like the ones that got screened had much earlier stage cancers, which you could argue is the effect of screening, but you could also argue it's the effect of length time bias.

Dr. Angela: Thank you so much for your time and insight into this topic. I would also like to open this up one final time to our medical directors. If there are any final comments or questions before we adjourn. Okay. Hearing none, I want to thank you all for your participation in this CAC. We very much appreciate your time and input. Again, I want to remind you to please also provide your comments and your ratings for the evidence pertaining to the various questions in writing. We will definitely have a transcript available and again, a reminder to the non-panelists as well that we do appreciate your input and responses to these questions as well. So, with that, we will adjourn this CAC for the molecular testing for risk stratification of upper gastrointestinal cancer. And I wish you all a wonderful afternoon.