Multi-Jurisdictional
Contractor Advisory Committee (CAC) Meeting

Meeting Date & Time: September 4, 2025, 3–5 pm ET
Topic: MolDX: Molecular Testing for Detection of Upper Gastrointestinal Metaplasia, Dysplasia, Neoplasia

Gabriel Bien-Willner 0:22

OK, sorry. So let me state again. It seems like we didn't start the recording process until now. I would hate to make it people restate that have already spoken their affiliation. So, let's just move past that. Again, this is being recorded.

Gabriel Bien-Willner 0:38

And let's move on. Thank you, Doctor Glover. I think you might have gotten cut off a little bit.

Jamie Glover 0:43

No problem.

Gabriel Bien-Willner 0:45

OK. Thank you. Next is Doctor Stephen Meltzer.

All right, let's come back to Doctor Meltzer. I think some people have to. Everybody's been muted and their camera's turned off unless they've selected that they agree to participate. Let's go to Doctor Prasad Iyer.

Prasad G. Iyer 1:17

Hi, good afternoon everyone. I'm Prasad Iyer. I'm a gastroenterologist, I'm professor of medicine and chief of GI in Mayo Clinic in Arizona I have a long-standing interest in Barrett's esophagus and have been fortunate to work with Doctor Shaheen on the American College of Gastroenterology Barracks Management Guidelines. Thank you.

Gabriel Bien-Willner 1:45

Thank you very much. So, I will also start to take a minute here and apologize for having multiple teams meeting links. We've had some technical difficulties for a few weeks not being able to record on some of these calls in the initial call that was set up, record function was not enabled for whatever reason, which is why we switched it. And it looks like Doctor Meltzer is on the other call. So as soon as it's confirmed that he's back on this one, we'll ask him to introduce himself as well.

Next, how about Doctor Amitabh Chak?

Amitabh Chak 2:26

I'm Amitabh Chak. I'm a professor of medicine here at Case Western Reserve, actually one of the three inventors of the technology that's become EsoCheck and EsoGuard.

That we'll be discussing also current president of ASGE and most of all I just followed Nick Shaheen and Prasad Iyer's guidelines.

Gabriel Bien-Willner 2:54

Thank you very much. How about Doctor Adam Booth?

Adam Booth 3:00

Hi, everyone. Thank you. I'm Adam Booth. I'm a gastrointestinal pathologist at Washington University in Saint Louis. Thank you.

Gabriel Bien-Willner 3:10

Thank you very much, Doctor Sachin Wani.

Sachin Wani 3:19

Hey, good afternoon, everyone. I'm Sachin Wani. I'm a gastroenterologist at the University of Colorado. I serve as the Executive Director of the Rady Center of Excellence, and I've also been fortunate enough to serve as an author on the GI Society guidelines for Barrett's esophagus. Thanks again for having me.

Gabriel Bien-Willner 3:44

Thank you very much and I hope you're not driving.

Sachin Wani 3:47

I'm not driving. Thanks for asking.

GABRIEL BIEN-WILLNER 3:49

OK. Otherwise, I would turn off your video feed right now. We don't want to see some horrific accident. And last but not least, Doctor Joanne Gibson.

Sachin Wani 3:51

Yeah. OK.

Joanna Gibson 4:07

My name is Joanna Gibson. I'm from Yale Pathology in New Haven, CT, and I specialize in both GI pathology and molecular pathology, and I'm a member of the Molecular Oncology Committee of CAP and I also happen to be Patient Safety Director at Yale. Thank you.

Gabriel Bien-Willner 4:30

Great. Thank you all so much for introducing yourself. Again, we're going to run through a series of questions. The intent of these questions is to get a dialogue going, but ultimately for us to better understand. Oh, yes, I'm sorry, Doctor Meltzer, will you introduce yourself? We're sorry, we explained that there was an error with the team set up and that you were stuck in the other, uh, in the other call.

You're muted, Doctor Meltzer. Can you unmute yourself?

Stephen J. Meltzer 5:01

Can you hear me now? OK, Stephen Meltzer, Johns Hopkins University gastroenterologist. I also have been involved in a non-endoscopic device study using a sponge retrievable sponge.

Gabriel Bien-Willner 5:03

Yes.

Stephen J. Meltzer 5:17

Inside of a capsule and some methyl DNA methylation-based biomarkers as well as prognostic biomarkers for biopsies from Barrett's patients.

Gabriel Bien-Willner 5:31

Thank you so much, Doctor Meltzer. All right with that, the introductions are done, I again want to reiterate that the goal here is to have a discussion around effectively the clinical context and opinions from experts on the evidence to date.

On the use of not just the devices, but the ultimate underlying tests that are being performed. And I wanted to start off with a very, I will say you're going to hear questions that you may hear the same questions stated multiple times. That's kind of by design. We want to make sure we cover some of this information from multiple angles. I want to start things off with a very simplistic question for the clinical folks here around the workup of patients for Barrett's esophagus and the question is and I hope you guys were able to see the questions in advance, I know there were some changes made in the last couple days, but we're going to go through these questions and again feel free to state if you want to say additional things beyond what's listed in this question, if it's good for the discussion. The question is what are the presenting signs and symptoms that would result from a patient that would result in referral for esophagogastric duodenoscopy or I'm just going to say EGD as part of a Barrett's esophagus evaluation and let's focus on the typical Medicare beneficiary population, if possible. And there's a couple components to this question beyond just what are the typical signs and symptoms. So, let's just start with a typical approach. Dr. Glover, I saw you raise your hand. If you want to kick it off.

Jamie Glover 7:20

Well, it just seems like it maybe it should start with primary care because that's gonna be the most common entry point for a Medicare beneficiary and, so, in my private practice where I do take care of all ages, including retirees on up to very old grandmas and grandpas you know, I recognize usually at like a Wellness exam the published risk factors. You know, I recognize when people have chronic uncontrolled reflux, intermittent reflux or I noticed in the medication reconciliation that they're on a chronic PPI type medication. So, it kind of starts with that.

And then looking at that age group, like just their age as a risk factor. I mean, these are all published, you know, often their sex, you know, male sex is 1, their weight, if they've been a smoker or are one now or smoke exposures, different things like that. And so, in the past that would usually be me starting out with that referral.

Recognizing like this is a person with a chronic symptomatic condition of reflux or needing control of with a PPI for that. And I would start the referral there for an EGD to a gastroenterologist to evaluate for Barrett's or you know, even esophageal adenocarcinoma

Nicholas J Shaheen 8:21

Mhm.

Gabriel Bien-Willner 8:37

Thank you, Doctor Shaheen.

Nicholas J Shaheen 8:39

I think that Doctor Glover's spot on. I just wanted to mention that we've had, there's really good data to actually substantiate these risk factors. There are, we kind of messed up our terminology as we were developing these guidelines and, that you usually think about a screening test being average risk, general population type people. But really when we talk about Barrett's, we're talking about and we say for Barrett's screening, we are actually talking about a high-risk population just like Doctor Glover mentioned. And really these risk factors have been recognized more or less by all the guidelines. There's some small differences in the way they're applied, but the bottom line is that there's really good literature to show that white race, GERD symptoms, male sex, people who are over the age of 50, tobacco users, obesity. Family history. Those are the things that pretty much all the guidelines endorse.

Gabriel Bien-Willner 9:37

Thank you, Doctor Prasad.

Prasad G. Iyer 9:39

Yeah, thank you. Maybe just an additional point I would like to raise. I completely agree with what Doctor Glover and Doctor Shaheen said. The one thing to also recognize is that these patients may have actually have no symptoms as such. They may actually even have well controlled reflux. And it is not just the presence of reflux symptoms that should drive the referral, but really gastroesophageal reflux symptoms, whether current or in the past. So, even if they are controlled on say a proton pump inhibitor, but they have not had a screening procedure, then we would still recommend that that be factored in as one of those five or risk factors that we have identified. Thank you.

Gabriel Bien-Willner 10:30

Thanks. I'd like to follow that up with another related question, which is yes, we understand the guidelines identify a series of risk factors, multiple of which must be present for the evaluation. The question is, are all of these guideline related risk factors considered equally in a decision to have an EGD referral?

Jamie Glover 11:01

I'm going to say again, since I'm the referrer, I mean it usually most often does start with me with either the fact that they're on some sort of anti-reflux medication, intermittently or constantly, even if it's controlled, so like a PPI, but they're not complaining a reflux. So, it usually kind of does start with symptoms for me. So, in a way that carries a bit more weight and then I look at all the risk factors and then it creates a risk factor profile for me and then I refer appropriate patients based on the guidelines.

Gabriel Bien-Willner 11:37

I think Doctor Wani had a question or a point. You put your arm down so.

Sachin Wani 11:40

Yeah, I just wanted to add, yeah, I just wanted to add that our guidelines don't necessarily make a distinction on the amount of weight that you should be assigning to each of these risk factors. But what is clear is that you've got to start with one basic prerequisite, which is the presence of chronic gastroesophageal reflux disease and then you need to have three out of the remaining 6 risk factors. Now granted, when you look at the odds ratios, the relative risks for the presence of Barrett's or esophageal cancer with relationship to each of these different risks' factors. They vary a little bit, but by and large they're pretty much needed at the same level.

Gabriel Bien-Willner 12:27

Thank you. And then moving past the referral process really quickly for making that that diagnosis of Barrett's esophagus, just a simple question. You'll see some of these questions might seem self-evident, but for some reason we also want things stated on the record. Is pathology required to make Barrett's esophagus diagnosis?

Doctor Shaheen.

Nicholas J. Shaheen 12:56

The answer is yes. In the states, you need two factors to get a diagnosis of Barrett's. You need a endoscopically evident segment of clonar epithelium in the esophagus that's at least a centimeter long and the biopsies of that tissue have to show us intestinal metaplasia So, if you don't have both those two components, you don't have Barrett's, and upper endoscopy should be able to with certainty tell you Barrett's yes versus Barrett's no.

Gabriel Bien-Willner 13:34

Thank you, Doctor Booth.

Adam Booth 13:39

And unmute myself. Yeah, I would just echo what Doctor Shaheen said there. Yeah, you do need Histology, so intestinal metaplasia So, it's required here in the states.

Gabriel Bien-Willner 13:40

Thank you very much. Let's go back to the referral process. And so again, Doctor Glover, you may be front and center here and I apologize if you have an outside role, especially on the earlier questions, are all the patients that are eligible under guideline for EGD referral or for Barrett's esophagus workup. Let's say that are all referred to EGD for the procedure?

Jamie Glover 14:21

So um.

I would say in my practice, yes, they are. I, you know, my referral patterns just reflect those guidelines we just talked about. And I do think it's pretty well publicized to family physicians at least, you know, and probably internus.

What those guidelines are now, I know there's probably barriers in that and so I'm sure it's not 100%, but I feel like most of my patients are referred. Is that what you're asking or maybe I'm not answering the question?

Gabriel Bien-Willner 14:55

Yeah, I'm asking well, so you've clearly stated that in your practice that everybody who qualifies under guidelines does get that referral. That seems to imply that not everyone does that. Is that a correct assumption?

Jamie Glover 15:11

I think most family physicians at the time of like a Wellness visit, and that's probably the number one thing, is making sure people get in for that. So, you have a moment to look at things that they may not even be complaining about to screen. If you can get them in for that, then I think most of us would be good at.

Referring and trying to get the patient to comply with that and we can talk more about that in future questions. I know it might address that, but yes, I do feel like based on guidelines, most of us are referring for EGD for Barrett's esophagus screening in appropriate high-risk patients.

Gabriel Bien-Willner 15:49

Thank you, Doctor Prasad.

Prasad G. Iyer 15:52

Yeah, thank you. While I congratulate Dr. Glover for referring more screen eligible patients, there are several of us on this call who have systematically looked at the data of how many patients were screen eligible are actually undergoing Endoscopy anyway, including Dr. Shaheen, Dr. Wani, Dr. Chak. And the data does seem to suggest, and ourselves at Mayo Clinic, the data seems to suggest that it's on a minority of patients who are actually eligible for screening.

Even using the criteria that have been published, who actually are referred for an endoscopy. So, if you the numbers range anywhere from 9 to 10% to a maximum of 39%, which I think Doctor Shaheen's group had reported.

So. I should say that only a minority of patients who are screen eligible are actually undergoing any kind of endoscopic evaluation at this point in time. And there's also a fair bit of data on what the barriers might be. And I see that there is a question.

Gabriel Bien-Willner 16:56

Thank you. Oh, go ahead.

Prasad G. Iyer 17:04

Beyond that, but I think that has been dissected as well. Thank you.

Gabriel Bien-Willner 17:10

Thank you, Doctor Chak.

You're on mute if you're speaking.

Amitabh Chak 17:20

Sorry, I was going to just reiterate what Doctor Iyer said, somewhere around 10%, maybe a little higher are actually getting referred for endoscopy of people who meet the criteria So yeah, we'll talk about the barriers, but or why they don't get the endoscopy, but most are not getting endoscopy.

Gabriel Bien-Willner 17:48

Yeah, we'll try to hone in on that in on the next question, Doctor Smith.

Michael S. Smith 17:57

Not to beat a dead horse, but I would just add that here in New York, even where patients are very pushy about getting as many things as they can to protect their health, we see similar results to what Doctor Iyer, Dr. Chak, Dr. Shaheen have mentioned. So, I congratulate Dr. Glover as well, but it is not the norm and we're much closer to that 10% number that's come up in prior studies.

Gabriel Bien-Willner 18:21

Thank you for that. So, let's now dive into that. I want to understand better, or we want to understand better where the problem lies and I noticed that there was there a comment about data and that this has been addressed in certain publications. I want to break this down into oh Doctor Dunst. Sorry you had a comment I missed. Feel free to speak.

Christy Dunst 18:51

Yeah, again, not to beat a dead horse, but a little, I do have a slightly different perspective. We looked at throughout our large health system in Oregon of all patients who had esophageal cancer, and we were operating on them, and we found that only 15% of them had had an EGD in the before their presenting symptoms with cancer, only 15% of them despite having had colonoscopy. So, it's a little bit different twist on what everyone else is saying is that the guidelines are clear, but in reality they're not getting it.

Gabriel Bien-Willner 19:34

Thank you. So, I want to then pursue this line of thinking a little bit more and kind of divide this up into two separate thoughts. One is the idea that patients may not be getting appropriate referrals, and the 2nd is non-competitive.

Clients on the patient's part. So, my first question is, you know, Doctor Glover's stated that she follows, and her practice very clearly refers all patients, but maybe from those others here who have experience with maybe multiple primary practitioners or family practice. Physicians, if they're aware or have any idea, or if there's any evidence to what may cause a lack of appropriate referral for eligible patients.

Jamie Glover 20:26

Now I do want to say one thing just as the referrer. So, just because I want to refer everyone that I identify and try to, I don't always enter the referral because if the patient isn't going to do it and they tell me that.

Then I don't even enter the referral and then seven years down the line or whenever it is that they find out they have esophageal adenocarcinoma It's not because I didn't try, but that it may be true that with all the things and maybe I don't know when to cross over into barriers to referral that need to be done in a Wellness visit and what is maybe the most important five and there's really ten things that need to be done. And that might be another reason why it might not be done at that year. Like what if I identify it that year that it should be done, but there's actually three higher priorities, you know, then that's the great benefit of a longitudinal relationship with a family physician. So, sometimes if something can't be done, then could it be done in six months, could be done in one year? I mean, you have to deal with reality. Ideally it would be done in the moment you identify the risk factors. But that's my reality in clinic and then, you know, maybe there's an.

Gabriel Bien-Willner 21:25

Sure.

Jamie Glover 21:40

Education piece still for family physicians about what is symptomatic GERD and does being on a PPI and having asymptomatic GERD at that point or intermittent GERD, does that count? So, I'm sure there's an education piece too out there. I happen to know a little bit about that, but there are other things in primary care that I might be weaker on, so I'm sure that's always a factor.

Gabriel Bien-Willner 22:01

Thank you very much for bringing that context. It can be very complicated. We try to distill things to yes or no, but sometimes it's more complicated than that for sure. Doctor Wani.

Sachin Wani 22:15

I'm so glad this is in your top three questions that you're bringing up, because this really comes down to addressing the main reason as to why we've not been able to make a dent on the epidemiology of esophageal cancer, right? This is something that's of great interest to us and we've actually looked at this qualitative, qualitatively and quantitatively and surveyed multiple primary care physicians across the country. And we've distilled this down to three main issues. One is lack of awareness of published guidelines, inability to identify risk factors and primary care physicians coding not having enough time to think about esophageal cancer screening and we published these data as a part of the screen being project that we conducted that was funded by.

Thank you.

Gabriel Bien-Willner 23:20

Thanks Doctor Wani. I think you were mentioning a publication, but you were cutting in and out. If you want to repeat that last statement, it would be helpful.

Sachin Wani 23:32

Yeah, this is a part of the Screen BE project that we published a few years ago in Gastroenterology.

Gabriel Bien-Willner 23:38

Thank you very much, Doctor Smith.

Michael S. Smith 23:43

Yeah, I would just add on to what Doctor Wani was saying is that we know that even if the referral is made, only about 40% of those folks who have the referral in hand actually get the upper endoscopy to complete the process. And you know that's the case not just for the Barrett's high-risk population.

We're talking about here, you know, we see that in colorectal cancer and other places as well and particularly with an aging population that's in the Medicare group that we're sort of focusing on today. You know, there are other health concerns that take precedence. There's reluctance to undergo sedation and other procedures. There's really sort of a gap where folks recognize that they may meet criteria but to them personally it doesn't resonate, and they don't go through with it. And I think Doctor Bien-Wilner, you were talking about that in the introduction earlier. So, you

know we really have to focus on the fact that just getting the referral doesn't get the patient over the finish line and that's a big part where we step down in terms of meeting the need here.

Jamie Glover 24:47

And so to piggyback on that with the patient compliance now because I was kind of talking about the physician side before, but I mean I have you know patients, I mean like one of the patients I've done a non-endoscopic on for example, he wouldn't go get the EGD because even though he's 72, he's still an engineer on wind turbines. He doesn't want the time off work. I mean I have

Gabriel Bien-Willner 24:47

I think.

Jamie Glover 25:07

Patients, they're afraid of procedures. They're afraid of sedation. No matter what I say, they just have general health anxiety. They're not symptomatic. So, it's not on their priority list because they are on their PPI. So, even though I'm saying I think this is a priority, they don't believe me. They like me, but they don't believe me. You know, there's the logistics of scheduling things. I mean, older patients, you know, they don't do portals very well. A lot of them, some do, but you know, they don't. There's texts, they miss the texts. You know, I don't know. There's so many issues with all of that. There's just procedure burden, like I mentioned before, like I might have to refer to an older patient for so many things and you know they can only do so many things a month. So just between, I don't know, time, the fears, the anxieties, the burden, you know, logistics that is, there's a lot of barriers to compliance and to lack of symptoms. So, patients really not prioritizing it because they don't. They don't feel it so.

Gabriel Bien-Willner 26:09

Thank you, Doctor Shaheen, and feel free to address both the barrier to referral as well as barrier to compliance, which the can of worms has been opened.

Nicholas J Shaheen 26:23

Yeah, I think some excellent points have been made and I especially appreciate Dr. Glover's perspective as somebody that's trying to get folks to do it. One thing that hasn't been mentioned yet that I did want to mention working in a rural state is that endoscopy facilities are not logically placed.

In the US and in fact when you plot out endoscopy facilities, we have endoscopy deserts and unsurprisingly people from oftentimes these rural areas that are looking at an hour plus drive to get there and then even with more complexity if they only have certain healthcare systems they can go to. No wonder that many of these orders, like Doctor Smith was saying, you know, folks just don't come in. It's just too hard. If you live in New York City, you're probably 20 steps away from an endoscopy on every corner. But that's not true in North Carolina

Jamie Glover 27:24

It's definitely not true here in Colorado with the mountain range and you know, big gaps. And I actually specifically did rural temp work where I would fill in for rural hospitals around this state when I was before I opened my practice to moonlight. And so I was in those places that would be in the farthest corner of our state next to Kansas and Texas. Nowhere, you know, Colorado.

And yes, definitely that would be a barrier for sure. The travel and taking time off your ranch, I don't know whatever that entails.

Paul S Panzarella 27:47

Yes.

Gabriel Bien-Willner 27:53

Thank you, Doctor Panzarella

Paul S Panzarella 27:56

Yes, I just kind of want to also echo and piggyback a little bit on what Doctor Glover was saying that for myself as a community gastroenterologist, you know we're on the front lines and seeing.

Amitabh Chak 28:10

But.

Paul S Panzarella, 28:12

Lots of patients here, which we're appreciative of all the referrals from the primary care physicians, but even we as gastroenterologists have that huge mountain to climb, especially with those who are asymptomatic or have well controlled GERD to convince them why they need something more invasive like an endoscopy. So that certainly is a challenge that I do see.

Gabriel Bien-Willner 28:41

Thank you. Let's move on. I want to get so we've addressed getting to the EGD and now I want to talk about the EGD itself. What are the current limitations of the traditional BE? And adenocarcinoma workup or surveillance by EGD. And what I want to understand is. Are there limitations in using EGD itself as a screening or surveillance tool and what those limitations could be?

For example, is there a known indeterminate result? Is there, you know, false negative rates, false positives, et cetera? Let's start with Doctor Panzarella I'm by the way picking you guys based on who raises their hand first. So, I'm not picking favorites. Doctor Panzarella

Paul S Panzarella 29:34

OK. I think to answer that question as concisely as possible is no, there are no indeterminate results when we're dealing with Barrett's esophagus.

Of course, it is a bit more of an invasive procedure that does require biopsy for confirmation, as our colleagues had stated earlier, but this definitely is something that not all patients are willing to go through.

Gabriel Bien-Willner 30:12

Thank you, Doctor Shaheen.

Nicholas J Shaheen 30:14

Yeah, I think we've already heard the biggest limitation, which Doctor Panzarella just referred to again, which is patients don't get it. You know, it's a good screening test that, you know, in fact the definition of Barrett's is made so that the screening test will not yield indeterminants.

The problem is, if only 10% of patients get any screening tests, we're not going to have effective screening for the disease.

Jamie Glover 30:39

And I don't know if I'm jumping ahead here, but that is you know to have like this you know non-endoscopic test that has binary result, positive, negative, I mean getting a positive on that in my experience.

GABRIEL BIEN-WILLNER 30:40

Thanks.

Jamie Glover 30:54

Really helps people go on to get that EGD, which I don't know. I just want to throw that in there. I don't know if this is the wrong time, but.

Gabriel Bien-Willner 31:01

I think you're. We are getting there. Don't worry, Doctor Iyer.

Prasad G. Iyer 31:09

Yeah, thank you. I just like to maybe re-emphasize what Doctor Shaheen said. In in my mind, it's the lack of access, the invasiveness, the expense of endoscopy, which to me are the biggest limitations of it being used as a screening tool and we know for the last two or three decades we've been advocating for screening endoscopies and now we have good data to know that only 10 to 20% of patients are actually getting screened. So to me that's a very, very strong argument.

Maybe with as a follow-up to Doctor Panzarella, the only thing I would suggest is, you know, if we see severe esophagitis when we do endoscopy, that's when we pause and we are not able to make a determination as to whether there is Barrett's or not, we would put a high-dose proton pump inhibitor and then bring them back after the esophagitis has healed. In my mind, that is a time when we would perhaps be pausing. But other than that, we know that if we actually take good care and do proper measurements and a good examination, we should be able to distinguish whether someone has Barrett's or not.

Gabriel Bien-Willner 32:29

Thank you, Doctor Chak.

Amitabh Chak 32:33

Yeah, what I was going to say is, you know, a burn endoscopy is a great test. It detects. It's how we detect Barrett's, because that's how you get biopsies. So, a pathologist can identify Barrett's. The problem is, like Prasad is saying, the incidence of this cancer keeps going up. It's the second cancer behind pancreas cancer. We've made great strides where we can actually prevent cancer, and that's really got to be the goal here. Even early cancer in the esophagus can be systemic, so you have to go to prevention and the only way to prevent it is if you could get people sparets detected. And the problem has been that even though we've been talking about doing upper endoscopy people for various reasons and Doctor Glover can talk about it. Despite being motivated, her patients won't go to it is that you can't get everyone to upper endoscopy to detect the Barrett's that they have when their GERD is controlled and furthermore just to add on to what Nick has said, we've looked in Ohio in our state and county to county. If you just look the death rates from this cancer are much higher in endoscopy deserts than they are in areas that have endoscopy now that may be a variety of different reasons that doesn't but yeah, endoscopy is a great test. It is just that people aren't getting endoscopies and doing something non-endoscopic does motivate people to get endoscopies.

Gabriel Bien-Willner 34:10

Can I? Before we go to Doctor Wani, who's the next in line here, I I'd like to ask one of the GI pathologists if they could comment on error rates or false negative rates? I mean you're sampling the esophagus, are you always sampling the right area? Do you have indeterminate results? Does that really happen? I think it'd be good for a diagnostician to comment on that if somebody can't comment on it.

Amitabh Chak 34:40

Hello.

Adam Booth 34:46

Sure. Hi. It's Adam Booth. You know, we don't have a like there's not a, you know, we have indefinite for dysplasia, but there's no indefinite for Barrett's, you know, so it's either yes or no, you know, we see the intestinal metaplasia or not.

Gabriel Bien-Willner 34:47

It's.

Adam Booth 35:02

And then regarding you know it's it as far as like tissue content seeing what we see.

You know, it comes down to basically how many biopsies fragments we get, the specimen quality, how fragmented is it. So, there can be a lot of variability in there. You know, that's kind of where that working hand in hand comes into play. I think Doctor Gibson maybe has something.

Joanna Gibson 35:29

Yeah, I 100% agree with what's been said. It, you know, we either see the Barret's or we don't and it's, you know, whether it's Barret's is seen on.

Adam Booth 35:30

To add.

Joanna Gibson 35:46

You know, the endoscopy grossly and what we see on the slides can be different depending on sampling error. And sampling error is a well-known phenomenon and it's a little bit spurious. It's not something that we can necessarily predict ahead of time that there's going to be sampling error.

So I think it's something to consider, you know, so, you know, a patient may have features of Barrett's esophagus, but the biopsy does not reveal any goblet cells. And so, what do you do with that patient? you know, we can only diagnose what we see and there's, you know, various tools that we can use for that, you know, for example, cutting additional sections or something like that and we definitely do all of those kinds of aspects from a diagnostic standpoint. But when the diagnosis is finalized, that's what it is and if we don't detect the Barret's we can't confirm it.

Gabriel Bien-Willner 36:43

Thank you. Thank you for that. Let's go back, Doctor Wani. Sorry to kind of take a short tangent there. Go ahead.

Sachin Wani 36:51

And. No worries, but I think the conversation that we just had is really relevant to what I'm about to talk about. I mean, just for the record, I think we should just clarify since you brought up two different terms in your question, screening and surveillance, right. So screening is what we're talking about.

Right now where upper endoscopy is the gold standard to make a diagnosis of Barrett's esophagus, surveillance is what we do when we do make a diagnosis of Barrett's and we bring them back periodically and that you already opened a can of worms in terms of the issues that we face with.

We do perform surveillance endoscopy, but I think we can just stick to what we're talking about, which is making that diagnosis of Barrett's esophagus. I wanted to add little bit to what Doctor Chuck just brought up about, again, going back to the whole idea of doing screening, it's to make this diagnosis of Barrett's esophagus detect early cancer and then ensure that these patients are treated with minimally invasive strategies, right? Screening has been around for even before I got into GI, so, I want to say at least about two decades that our guidelines have recommended screening. And if you look at the SEER database, still the proportion of patients who get diagnosed with localized esophageal cancer has not changed. If you look at that graph, we've made 0 dent on that number of patients with localized cancer. Thank you.

Gabriel Bien-Willner 38:34

Thank you, Doctor Meltzer.

Stephen J. Meltzer 38:37

Yes. So, at the risk of being a little bit provocative, I think there's an elephant in the room here that nobody has mentioned and your question asks about indeterminate results. So as a recipient of non-invasive or prognostic and non-invasive tests of patients who are referred.

For these tests, what I am seeing a very high proportion of are endoscopies by community physicians that are showing what they call Barrett's esophagus, which does not meet the strict definition of the expert endoscopist. So typically, there'll be a fuzzy Z line. They talk about an imprecise Z line and they biopsy it. I know they're not supposed to, but they do, and they find goblet cells and always at the end of Doctor Booth's report or Doctor Gibson's report, it says. If this biopsy was taken from the tubular esophagus and I quote Shaheen 2022 or Shaheen 2016 or both, and therefore they absolve themselves of responsibility, but the patient has been managed in many cases for years under surveillance as having Barrett's esophagus. So, you asked about indeterminate results. I think this is a significant problem in the community.

Gabriel Bien-Willner 40:01

Thank you for that perspective, Doctor Smith.

Michael S. Smith 40:07

Yeah, I just wanted to go back to the screening surveillance piece that Doctor Wani was talking about because I think that's really important. But remind everybody who's listening that again, this is not like you turn 45 years old and everybody gets a screening colonoscopy for colorectal cancer, right? This is only for an enriched high risk symptomatic population where the symptoms and the demographics meet the criteria to confirm a high-risk status that then leads to the recommendation and the guidelines for screening. Of this high-risk population, it's not that average risk screening. I know we mentioned it before, but I just want to make sure that we ground ourselves with that. We're not talking about the whole population. This is a select high risk population that has the combination of the symptoms and the demographic factors that lead to that recommendation.

Gabriel Bien-Willner 41:02

Thank you. I think we are aware of that. I think you know payers typically have a definition of screening that is not consistent with how it's being applied here. So just we understand that is understood. I think Doctor Gibson wants to comment on Doctor Meltzer's comment. Go ahead.

Joanna Gibson 41:20

Yeah, I just wanted to add a little bit to it. I mean, he's not wrong in how he interprets this, but I think from a pathology standpoint, it's been shown in many studies that when we're given a biopsy from around the GJ or lower esophagus, there are very few anatomic. Mescopic landmarks that we can use as determining that this biopsy came from the tubal esophagus. And so that's why we end up writing these comments and I think it's, you know, we do have to put it back into the endoscopist hands to make that correlation.

Stephen J. Meltzer 42:05

Yeah, I wasn't meaning to criticize you, Joanna Yeah, what I'm saying is this is a large number of patients and it's not being mentioned. And in the referral for these tests, particularly the prognostic test, I'm seeing maybe 30% of patients who do not.

Gabriel Bien-Willner 42:06

Thank you, understood.

Joanna Gibson 42:09

No, I did not feel criticized.

Stephen J. Meltzer 42:24

Not meet the criteria for the strict diagnosis of Barrett's, but they're being treated that way in the community, in some cases for many years. And I think when you're asking this question about indeterminate results, I think indeterminate results are a large problem.

Gabriel Bien-Willner 42:41

Thank you, Doctor Panzarella. Let's close out this line of thinking with Doctor Panzarella in the interest of time. Go ahead.

Paul S Panzarella 42:46

Sure, I think for sake of discussion being on the community GI side.

You know this is this is something that we do see very commonly, and I think to the best of our ability we do try to biopsy appropriately. We do understand that like Doctor Booth was saying before that it is positive or negative, you know, either you have it, or you don't. But certainly, as community GIS, we certainly are trying to advocate for our patients, not mismanage and try to capture as many people as we can to try to prevent the disease from progressing.

Gabriel Bien-Willner 43:33

Thank you. I'd like to now move on from the pre-test patient evaluation and the pitfalls and obstacles in the pre-test. I want to now start talking about these kinds of tests and services and so I very carefully worded these statements. So feel free to ask questions If you'd like, but I would like an answer and again a multi-part question, but let's start with the first one if there is a non-invasive or minimally invasive test that could reliably identify patients who are not likely to have Barrett's esophagus or worse, just other dysplasia or adenocarcinoma And let's call this a rule out test. How would such a test impact your management of the patient.

Start with Doctor Panzarelli.

You got the last one, you get the first. You got the last word before you get the first word now.

Paul S Panzarella 44:30

Hi. Thanks for the opportunity. I think this is a great question.

Again as a community gastroenterologist, you know we see a lot of patients for a multitude of reasons and granted some of those referrals are the patients that are directly referred for GERD. And sometimes these are patients that we are seeing for colorectal cancer screening and just incidentally notice ourselves that they've been on long-term PP is or attest to certain GERD symptoms. Now you know they say for example they're there to see us.

For a screening colonoscopy consultation, but now we bring up GERD. Of course, that now gives us the opportunity to come from an advocacy standpoint to look out for that patient, not only from a colorectal cancer screening perspective, but also

having the potential to detect a precancerous condition of the esophagus. So, having something that's less invasive I think has now become something that I've been able to incorporate into my practice very effectively to try to carry that message across.

To the patient, I love to make sports analogies to help patients understand what I'm talking about. When I speak about mortality with colorectal cancer screening, it's about 50,000 people a year.

Which equates to a baseball stadium. And if we're thinking about esophageal cancer, we're thinking about an NBA arena, and I feel that those things resonate with patients. They may not always be willing to do something like a second procedure.

Because like several of the of our colleagues had stated before, we have to be also mindful of cost to the patient as well. And if we had something less invasive, I think that could certainly drive the point home as to why we would advocate for something like that.

Gabriel Bien-Willner 46:37

Well, let me push you because I feel like you didn't actually answer the question, which is now again presuming that this is a reliable test, and you can interpret whatever that means if you get a test that you believe reliably identifies the patient.

Paul S. Panzarella 46:49

Mhm.

Gabriel Bien-Willner 46:55

Paul is not likely to have Barrett's esophagus and you're evaluating a patient for, you know, Barrett's esophagus. How would that information impact or change the management of that patient for you?

Paul S. Panzarella 47:12

I think with regards to that specifically, if I have something that's non-invasive that has great data behind it, such as this, when I think about screening tests.

For my patients, I want something that's going to be reliable and give me very low false negative results. So, something such as this type of testing if this test, which it does come back negative. We can say with 99% certainty that it's truly negative and that means a ton to me as a gastroenterologist, and I think I can convey that to my patients very well. And what that essentially translates to is that they do not go on to get an endoscopy.

Gabriel Bien-Willner 48:01

Thank you. Yeah, that was the question. All right. Anyone else have a comment? Yeah, Doctor Chak.

Amitabh Chak 48:11

Yeah, I think the way to think about it is you want a test that's sensitive and specific enough where you can rule out the disease with confidence so that if you do the test, you're 99%. Confident that that patient doesn't have Barrett's or cancer and doesn't need an endoscopy, and it's good enough that the patients who then are positive and get sent for an endoscopy. Your yield in endoscopy is going to be higher. Right now what we do maybe at 10, you know, based on our clinical and guideline scenarios, 10% of our endoscopies find Barrett's and 90% of the endoscopies we do don't find Barrett's.

So if you had a test that increased your rate of detection of Barrett's, made sure the people who have a negative test, you reliably feel confident that they don't have Barrett's, you're not missing cancer.

And the ones you send get enriched for endoscopy. Your endoscopists are happier because 30% of the time they're finding or 40% of the time they're finding barriers. The patients are happier because when it's negative, they can feel confident that.

Referring for the primary care physicians are happy when it's negative because they're not missing anything and for screening you don't have to do it multiple times. So, you know that's the characteristic you want in a test is you want to confidently rule out the disease. And then that enriches the population that you send for endoscopy that when it's positive is the way I think of it.

Gabriel Bien-Willner 50:01

Thank you, Doctor Shaheen.

Nicholas J. Shaheen 50:03

One thing I think is important to recognize here is that this is an unusual clinical situation in that if the test is falsely positive, they get the screening test that we were recommending anyway. So,

the whole ball of wax, I agree with Doctor Panzarella the whole ball of wax here is the negative predictive value.

If you can get this test and if it's negative, you're done, you're not going to scope them. The PCP is going to be happy. The patient is going to be happy. If you get the test and it's positive, like Doctor Chock was saying, you're greatly enriching that group for having something when you scope them, which is terrific.

But even the downside is not compared to a lot of other tests we do, isn't so horrible because they get the tests we wanted them to have in the 1st place. It's not ideal. And we're lucky that this test has a sensitivity north of, you know, eighty-five, 9%. But even if it didn't they're getting the test that we would have done anyway, which is about as low risk a test as we could refer to. So, the fact that this thing's carrying around a huge negative predictive value means that it's doing exactly what you want it to do because it's ruling out disease.

Gabriel Bien-Willner 51:09

Thank you. That was very clear. Doctor Iyer.

Prasad G, Iyer 51:15

Yeah, thank you. I think a lot of good points have been made. I maybe want to make another point in the sense that Barett's is while we talk of Barett's as a single entity, it's really not a single entity. So, you have non-dysplastic Barrett's, you have short segments non-dysplastic, long segment non-dysplastic, you have low-grade, high-grade cancer and really I would also posit perhaps that the sensitivity of the test should be higher for dysplastics and cancers.

Those are the patients that we really don't want to miss. So, there's going to be some heterogeneity in the performance characteristics of these tests, but as long as we are picking up the kind of Barrett's cases where we can intervene to prevent cancer, like high grade dysplasia or maybe low-grade dysplasia or pick up cancer, that's where we'll see the biggest impact.

Gabriel Bien-Willner 52:16

Thank you, Doctor Glover.

Jamie Glover 52:18

So when I was first presented with this rule out test and I was an early adopter Isa Garde specifically, I was really impressed by the negative predictive value of 99% and so I.

Amitabh Chak 52:24

Yeah.

Jamie Glover 52:34

Feel confident in those negatives and with that kind of you know published data and I feel comfortable managing those patients and continuing to do risk factor screening over the years and referring them again if appropriate but so that was

published piece, that NPV of 99% was what really swayed me. And then the second part of that question listed there is, you know, what other data I guess or something like that. But anyway, so, I told you about the issues with adherence and compliance to referrals and the other piece of data that impressed me, was that over 85% will complete them if they have a positive. And I know we're talking about the negative right here, but you know, those kind of things like play off of each other. So that's why we adopted it, I know, but that's why I adopted the test. So anyway.

Gabriel Bien-Willner 53:20

You guys gotta stop getting ahead of me. Yeah, no, no, thank you for that. I'm going to pin you again in just a second because I want someone to address another part of this. And I know you mentioned a specific test. Let's just, I want to stay kind of a high level first, like a theoretical test 1st and then we can get to the specific details.

In a minute because I don't want to conflate any specific service with the idea of what the value of these kinds of services could be. Doctor Dunes, you had a comment.

Christy Dunst 53:57

Oh, I was also kind of moving toward the opposite of your question. So, we'll wait. Sorry.

Gabriel Bien-Willner 54:04

OK. Now thank you. So at the highest level, right, you've got a test that you believe meets some

criteria for its quality, its performance as you mentioned what that could be in a patient who's being evaluated for Barrett's esophagus and If you had a negative result, would you still feel compelled to perform or to or to refer someone for EGD? That's yeah, I really wanted to drive that first towards you, Doctor Glover.

Jamie Glover 54:41

Yes, I based on the published data and the literature on these types of tests, I would not feel compelled to refer them on to EGD if there was a negative test with that high of a negative predictive value, so I could save that invasive test and continue to manage that patient myself until, you know, whatever point in the future, so.

Gabriel Bien-Willner 54:56

Thank you, Doctor Smith.

Michael S Smith 55:04

Yeah, the program that we're working to set up with our primary care colleagues at Mount Sinai and others that are up here in in New York, very much go on the exact same thing as what Doctor Glover said. If the test is negative, you're done. Save the resources for the people who really need them with such a great NPV of 99%.

Just, you know, that's the mic drop moment. There's no need to discuss it any further from our perspective.

Gabriel Bien-Willner 55:32

Thank you, Doctor Chak.

Amitabh Chak 55:35

I was just gonna add, there's already published data that show when non-endoscopic tests are negative, patients are not being referred like over 90% of them, but they're only being referred for other reasons. So, they don't get endoscopy and that's now thousands. And the other part of it is you'll get to is we can't resist talking about when it's positive, but when it's positive, like Dr. Glover said, they are getting an ask that motivates them.

Gabriel Bien-Willner 56:07

Understood. And that. I do have a whole separate question on that. Let's see if we can hold off from getting there quite yet. You mentioned Dr. Chak; I just want to follow up on one statement. You said that they would be referred for other reasons. Can you elaborate a little bit on what those other reasons could be. Go ahead.

Amitabh Chak 56:29

Well, if subsequently, say, a patient's found to be anemic or they've got dyspepsia or some other reason to have a, you know, there's multiple other reasons to do endoscopy. We live in a world where we just think of gastroesophageal reflux as one indication, but there are other indications that patients have for getting upper endoscopy and so, some patients end up getting upper endoscopy later.

Gabriel Bien-Willner 56:57

Thank you, Doctor Dunst.

Christy Dunst 56:59

Yeah, I think it's important to distinguish between another reason for an endoscopy and this situation, because if a patient was going has an indication for an endoscopy, whether it's anemia or you're worried that they have, you know, complications from a hiatal hernia or whatever, if they have a reason for an endoscopy.

Then they won't get the screening test because they're going to get an endoscopy anyway, you know. So, these are people that, you know, the primary care physician has heard about the guidelines, has heard about, you know, they have a patient that comes in and they're afraid because they had a friend who died of esophageal cancer and they're afraid and they're not otherwise going to get a scope. This test is hugely reassuring. It's so important because it has such a high negative predictive value that we can really hang our hats on. You know what?

We did, we did the highest-level test we can do right now and reassure the patients and reassure the PCPS that they have also done everything that they need to do to get to screen them out. I think it's really, really important than the negative predictive value.

Gabriel Bien-Willner 58:10

Thank you. Thank you for that. I want to stay kind of at a high level and kind of jump to the next question and then we'll come back to the middle part of this question in a minute. So, we talked about that's hypothetical like a reliable test and I want to now understand. How you would evaluate a test to determine whether it's reliable, what kind of information, what would I know you mentioned before 99% specificity. Where would you set a threshold for performance or quality for you in the evaluation of? Let's assume you've got it. We've got a lot of information here from. It seems to be fairly consensus that if such a reliable test could identify patients who are not likely to have their esophagus, that you would then not do a referral for EGD. OK, at which point I'm trying to. What I want to understand is that threshold where you would say this test is or is not good enough for me to decide not to do an EGD. What do I? What do you need to see from such a task to be convincing enough, can you formulate whatever that boundary condition is that would lead to say, you know what, this is good enough.

Doctor Shaheen.

Nicholas J Shaheen 59:36

I think it depends on the role that the test is playing. The test that we've been talking about now is essentially a rule out test. OK, that's what we're using it for. So, the one thing and especially in this situation where

Gabriel Bien-Willner 59:42

That's right. Let's focus on that.

Nicholas J Shaheen 59:53

The potential risk of a false negative, IE unresectable terminal cancer, is so much worse than the risk associated with a false positive.

I think you really need to see an NPV that's north of 98, certainly north of 95, but more like north of 98% because the first time one of these patients comes back to a practice like Doctor Glover's after a -1 of these tests and then has cancer, that clinician's never going to use that test again.

Amitabh Chak 1:00:18

OK.

Nicholas J Shaheen 1:00:29

And for some reason. So, I do think that, especially in this setting, that number has to be way up there. What exactly? You know, I think that everyone has some different feeling you can do decision analysis, but the bottom line is that I think that most people would want it to be. You know, certainly north of 95.

Amitabh Chak 1:00:50

Oh.

Gabriel Bien-Willner 1:00:50

Thank you. I think that decision analysis is kind part of what I'm looking for in this question, Doctor Meltzer.

Sir.

Stephen J. Meltzer 1:00:58

Yeah, so of course in principle I agree with Nick completely. However, I can point out that the current tests, non-endoscopic tests typically have A PPV of about 35 to 40 when they're the best. Whereas NPV is heavily influenced by the prevalence or incidence in the population, with Barrett's being so rare relative to, say, hypertension or other diseases, you're going to get a pretty good NPV most of the time with a typical molecular test.

It's much harder to get to the plus 90 level on PPD. So, I again I would like to make the distinction between premalignant or dysplastic disease and non-malignant disease. So, for malignant disease, yes, I think really it's extremely important to have A high PPV but for Barrett's the current sensitivity for screening is close to 0 since screening is not widely performed. So, any improvement above 0 in sensitivity for non-dysplastic Barrett's is helpful clinically and you may end up with a PPV of 30. I'm sorry, you may end up with a sensitivity of only 80% or even less, and that's still beneficial.

Gabriel Bien-Willner 1:02:21

Thank you, Doctor Meltzer. What I'm interpreting from your comments is that NPV is probably not the best value for making this determination, but sensitivity may be a better value. Is that fair? Go ahead.

Stephen J. Meltzer 1:02:34

Well, I was, I was making two points. One is about NPV and specificity. And so, specificity might be more useful than NPV because NPV is going to be inflated by the incidence in the population. The other point, though, was when I'm talking about sensitivity or PPV, it's important to distinguish between malignant and benign disease.

Gabriel Bien-Willner 1:03:01

Thank you, uh, Doctor Iyer.

Prasad G. Iyer 1:03:05

Yeah, thank you. I think this is an important point in my mind. As proposed to my earlier comment on Barrett's not being a single entity, I do feel that.

Whether it be NPV, whether it be sensitivity, NPV is obviously affected by prevalence, but we may have to look at the disease in different categories, particularly malignancy. Dysplastic Barret's and then non-dysplastic Barret's. The implications of missing each one of these three different categories is different, and as you read in the literature, you'll see some variation in the way the sensitivity is across these disease groups. And of course, their prevalence is different as well. So, a high NPV, high sensitivity for cancer and say this plastic Barret's is critical in my mind.

Amitabh Chak 1:03:54

OK.

Gabriel Bien-Willner 1:04:05

Thank you. That was very clear, Doctor Smith.

Sorry, Doctor Meltzer, I think your hand might still be up from your earlier comment. And if you raise your hand again, let me know. OK, Doctor Smith.

Amitabh Chak 1:04:15

OK.

Michael S. Smith 1:04:19

Yeah, I'm, I would just, I think it's that's true that there are different varieties of Barrett's and we're talking about the presence or absence of dysplasia and the grade of it, the segment length are different ways that we categorize the disease, but even the ones who that are considered the most benign that often make up the vast majority of the population, that's where a good amount of the cancer ultimately comes from. Half of the patients who develop esophageal adenocarcinoma had a prior endoscopy that diagnosed them with non-dysplastic Barrett's esophagus, so

to sort of say, well, we need to focus on the dysplasia detection and the characteristics around dysplasia is I think leaving out A significant portion of the pot in the group that's being given this test, because you want to make sure that you find the ones who are ultimately going to make up half the pot of the cancer is that,

would you know you're trying to prevent here. And I think that's also true for short segment disease. And there are a lot of folks out there who sort of say, well only if you have a longer amount, a larger amount of diseases that are really important. That's the vast majority of the population we're looking at here about 70% I think. And so, you know looking at the performance characteristics and these more.

Sort of benign versions is critically important from my perspective too. Sure, more intense stuff is important, but you've got to look across the spectrum of disease and I think it all is really critical here because the numbers game gets you to the point that that stuff that's categorized as less worrisome ultimately makes up a very significant port of the dangerous pot down the line.

Gabriel Bien-Willner 1:05:58

Thank you, Doctor Chak.

Amitabh Chak 1:06:00

Yeah, I would go back to the clarity that Nick talked about, which is you've got a rule out test when you're applying, when Doctor Glover is applying that rule out test into that at risk population.

That has a certain prevalence. She wants to be confident. The primary care physician wants to be confident that they're not missing something, and 99% negative predictive value is probably what you want.

To be very confident, even 98% may get you a little bit queasy, but you don't want to go any further South from that. You want a rule out test to rule out the disease and it's a rule out test. Now in terms of what it picks up when you do endoscopy, you want to pick up everything.

That we normally pick up at endoscopy. You want to pick up the short segment Barrett's. Yeah, they're not at as much risk, but there's a lot more short segment Barrett's out there. And if you look at the cancers that ultimately develop, like Mike was saying, they develop out of a fair proportion of them develop out of short segments. So you don't want to miss the short segment.

Yeah, you want to find the dysplastics because that's where you're going to intervene, but you want to identify all stages, whether it's short segment barriers, whether it's long segment barriers, whether it's low grade dysplasia, high grade dysplasia, and you don't want to miss the cancers.

But that that's later. The first thing is it's a rule out test. You want that high negative predictive value and that's what you've got to be driving. The rest of it, yeah, the positive predictive value, if you can get it up to 20%, great. That's more than we do with upper and Dow's, if you can get it up to.

30% even greater. That's better than current practice. That's a lot better than current practice and those of us who do endoscopy, but you want that negative predictive value because it is a rule out test.

Gabriel Bien-Willner 1:08:04

Thank you, Doctor Chak. Dr. Dunst, you had your hand up and you brought it down. Do you want to move on, or do you have a comment?

Christy Dunst 1:08:12

I just want to reiterate that first of all, the patients aren't being seen or they're not being seen at all. And I want to also reiterate what Nick was saying about the high negative predictive value. I don't think that we would be having this conversation if there wasn't.

To potential for the technology to be in the 9899 range. So, it sounds like we're in consensus to answer your question.

Gabriel Bien-Willner 1:08:42

Thank you. All right, let's kind of now go back and I want to address the middle half of the fifth question and also kind of the 9th question which is regarding this hypothetical rule out test, do you feel like there are currently tests on the market that that?

That meet what you would consider to be a reliable test in the ways that have been described and if you could also comment on the evidence or the, you know, the specific studies that have pushed you over the edge and deciding that.

A threshold for reliability has or has not been met. I know that now this is really the meat of where we're going, but I think it's time to kind of start discussing it now that we've kind of laid out the premise here, I think pretty well.

No comments.

Doctor Shaheen.

Nicholas J Shaheen 1:09:44

I think the ESA check and ESA guard system show the operating characteristics that we've all been discussing you've got multiple studies showing a big negative predictive value.

You're increasing the yield of the endoscopy. One thing that we haven't talked about as much about is that there's the screening population. I'm doing air quotes cause it's not a truly average risk population has a prevalence of disease of 10%. This is a very enriched group when you compare it.

To somebody walking down the street, if you get a positive EsoGuard, you have somewhere

between 2 1/2 to four times the likelihood of getting a positive upper endoscopy. So you're using your upper endoscopy much more effectively.

By putting this test in front of it, the average endoscopist is going to get a lot more yeses when they like scoping someone that has had this test and this is one of the reasons why I think that we as gastroenterologists, you know many gastroenterologists are worried about this taking their business and all this kind of hoo-ha that people here, we should be endorsing this because the biggest point, which I mean this is a horse that has been beaten quite dead, but we'll say it again, is that 10% of people that get this test, that need this test are getting this test. So, if this opens the top of the funnel and compels patients to come in when it's positive.

This is money well spent.

Gabriel Bien-Willner 1:11:24

Thank you for that. Let's see, Doctor Smith.

Michael S. Smith 1:11:27

Yeah. So, I'd like to address this question in my role as the president-elect of the AFS, the American Foregut Society as I mentioned in my introduction. Now again this is a group of 800 or so gastroenterologists and foregut focused surgeons who really focus their clinical.

Practices and their research efforts on diseases that affect the esophagus and really in particular gastroesophageal reflux disease and its complications, including Barrett's esophagus and esophageal adenocarcinoma And we published a position statement letter of support for EsoGuard and ESocheck.

And that technology is based on the strength of the published evidence and data and the perceived clinical utility. And I'll I want to just highlight a few things that were in our letter that came out based on how we viewed the technology again, you know its ability to enrich the patient population that's undergoing confirmatory endoscopic.

Testing and improving the yield of endoscopy as we've talked about before, its ability to be used as a point of care test in the primary care offices and it's, you know, it's ability to really expand out to providers who right now aren't able to provide screening and just with the strength of the data that.

Paul S Panzarella 1:12:31

Right.

Michael S. Smith 1:12:46

That's there, you know, this really is a no-brainer from the AFS's perspective. You know, you've got 10s of thousands of patients who've undergone ESO guard testing so far. The performance has really been excellent. The ability to collect the cells for analysis is a breeze.

Amitabh Chak 1:12:47

OK.

Michael S. Smith 1:13:01

The utility is very clear to all of us who have read what's out there in the published literature. Those of us who are working on studies that should be coming out very soon that have shown you know again very large populations that corroborate the data and expand showing those very high performance characteristics in a real-world setting.

And just being able to be to find these patients and prevent cancer by leading them to endoscopic eradication therapy when dysplasia is detected, you know all again in that are consistent with guidelines that are out there right now and what is considered best practice in our field and the only thing that's really been stopping us from doing more of this work to prevent, you know, this terrible cancer is lack of insurance coverage. And so, you know, to us the benefit is tremendous, the need is tremendous and the benefit to risk ratio is remarkably high. And so, I want to make sure that everyone understands that a group of people who do this for a living day in and day out feel extremely strongly that all of those pieces contribute to why we think it needs to be out there for our providers and for our patients.

Gabriel Bien-Willner 1:14:12

Thank you, Doctor Panzarella

Paul S Panzarella 1:14:15

Yes, I think just to further contribute to that, that EsoGuard is something that I incorporated into my practice for probably the past two years and the number of patients that were able to screen and find positive results who ultimately went on to have positive biopsies has been essentially game changing in my practice. These were patients that may or may not have been screened previously.

And I think, you know, from my own cohort of patients, it has certainly made a huge believer in me that this is something that we routinely do in my practice, something that I believe in wholeheartedly enough to really.

Given my all supported 100%, so much so that you know with a particular patient of mine that came in for a routine colonoscopy screening, filled out a questionnaire in our office that identified him being at risk and long story short had a positive EsoGuard positive biopsies so, now we are surveying him and he's on proper treatment and he was even agreeable to participate in the story that became a national news story.

Gabriel Bien-Willner 1:15:39

Thank you, Dr. Wani.

Jamie Glover 1:15:41

Hey, Dr. Wani, do you want to go together on this one about Dan?

Michael S. Smith 1:15:43

Y.

Sachin Wani 1:15:47

Oh, sure. I was, I was actually going to 1st. I'm happy to talk about our common patient as well. But before that, I think to go back to your question, are we there yet? Do we have enough data to say yes, this is ready for prime time? I think the biggest.

Jamie Glover 1:15:52

Oh, yeah, yeah.

Sachin Wani 1:16:07

Endorsement to the use of these non-endoscopic cell collection devices is what our GI Society guidelines have stated, right? So, the guidelines that Nick, Prasad, myself, we worked on, these are not just based on our emotions or how we feel about the cancer, this is really just based on the available evidence. We used a great framework to whether the data available for these technologies meet the bar or not, and it obviously does, and that's we've provided an endorsement for the use of these non-endoscopic cell collection devices.

Is all the data that Nick just brought up and we have data from a large randomized controlled trial as well showing us that you can detect more Barrett's esophagus, which is the precursor for esophageal cancer and at the same time you detect more cases with Barrett's related dysplasium and cancer. And just to add to this, because of the role that I play at my institution at the University of Colorado, similar to what Smith pointed out, our institution has also now incorporated non-endoscopic cell collection techniques within our PCP offices.

Amitabh Chak 1:17:25

OK.

Sachin Wani 1:17:28

And we offer it within our GI clinics. And again, we had to provide evidence to support why we should be using this in our practice. Doctor Glover, I'm happy to corroborate your story.

Jamie Glover 1:17:45

OK, so you know, have I used any such test? I have. I have incorporated this into my practice based on what I felt was a great negative, you know, predictive value as well as an acceptable sensitivity. So, I just wanted to bring up, like I mentioned before, the difficulties even when a family physician does recognize the risk factors in getting a patient to actually get a screening for Barrett's esophagus. And so, when I heard about this test, this non-invasive molecular test, I immediately could think of my first two patients that I needed to screen and one of those was Dan and he has allowed us to share his story and he, you know, had symptomatic GERD on PPIs, but not even controlled. And I knew that about him and it was, you know, I was seeing him for something else. I don't remember if it was his wellness visit or something else, but you know, I saw

the PPI there in his Med list. And I remembered how I had to help him in the middle of the night one night with his terrible Gerd that he was sitting on the edge of the bed with. And so, you know, looking at him, his age, his race, his weight, the fact he used to be a smoker, he's had smoke exposure in the military.

You know, I was like, hey, we need to refer you out for Barrett's esophagus screening. But Dan, I know you if I could show you right now a screenshot of my list of things I've referred him to that he hasn't done, it's like 14 things long and one has been completed. For some reason he doesn't like doctors. He doesn't like going to clinics. He's willing to come to his doctor in my clinic. It doesn't scare him here. He's not anxious about it. He does not complete referrals, and I have a ton of patients like that. That's why I said when I heard about this test, I immediately thought of like my first two patients. And so, I said, hey, what if we could do this screening here? We could bring in. Now we weren't trained to do this on our own yet, but we could bring in a nurse who's trained to do a non-invasive test here. And he thought about it and talked to his wife, and he agreed to do that because he did not agree to do an EGD.

And so we did the EsoGuard on him and another patient. That was my first two that I did and his was positive, the others was negative. I did not refer to the other patient for EGD. I was able to use the positive for Dan.

To refer him on to EGD to a local GI in my town of Colorado Springs, where they did discover on biopsy early-stage esophageal adenocarcinoma and then we were able to refer him on to Doctor Wani at the University of Colorado for mucosal resection. And so, it just really shows. It was a rule out test for that first one of two patients, the other patient and for Dan it told me he needed further, he needed diagnostic test, and I was able to use that to convince him to go to help him be adherent and it worked out well. So, I'll.

Jamie Glover 1:20:41

leave it to you, Dr. Wani.

Gabriel Bien-Willner 1:20:43

Thank you. If I could just move on because we've got about 30 minutes left and we still have A few more questions, but if I could just recharacterize some of what you said in a formulaic computer language that my brain speaks.

Jamie Glover 1:20:49

Oh, sure, sure.

Gabriel Bien-Willner 1:20:58

Would you agree that your statements are such that not only did you believe these tests can identify patients in your experience who do not merit or and do not subsequently get EGD? but the process of we talked about non-compliance on the patient side that a result, a positive result also seems to result in a potentially a decrease in the non-compliance.

Jamie Glover 1:21:16

Yes.

Gabriel Bien-Willner 1:21:33

Of EGD referral.

Amitabh Chak 1:21:34

OK.

Jamie Glover 1:21:36

Yes, that is true. So true to both statements. But do you want me to repeat what you said to make it a better sound bite or anything for the recording or OK, wait, will you say that in two parts now? Say they first ask me again. Oh yeah.

Gabriel Bien-Willner 1:21:44

Sure, yeah, if you want.

No, I don't. Somebody can play it back if they want.

OK, uh, Doctor Smith.

Michael S. Smith 1:21:57

Just very quickly, I have multiple patients that we screened from our fighter firefighters here in New York who have high rates of reflux and they are generally young, healthy people who don't expect to be needing healthcare because they're pulling people from burning buildings and when we did this drive and we had them turn positive and they had originally said I would never get a an endoscopy, the positive test came back and they have all come to us now after talking with us and or the primary care Doctor who the result was shared with 100%. It absolutely changes minds of patients, and they need to get the endoscopy done.

Gabriel Bien-Willner 1:22:36

Thank you. All right. This is a good segue into the second half of the original question of the rule out test. Let's talk about rule in and what these tests can do for rule in. If you could identify, let's go back to a hypothetical circumstance and then we'll get into the details in a minute, and this can be a shorter conversation because I understand this isn't the main rationale for why these services are used today. But it's good to understand your thinking on the other side of this coin, which is if there were a hypothetical test that was minimally or non-invasive.

Gabriel Bien-Willner 1:23:13

That could reliably identify patients who are likely to have Barrett's esophagus or dysplasia or adenocarcinoma and let's call this a rule in test and you believe it to be reliable. How would that impact your management of any given patient?

I guess the question is would you manage them any differently because otherwise you would also refer without this test, you would also refer them for EGD, or would it actually change your behavior towards that patient Doctor Dunst?

Christy Dunst 1:23:49

Yeah. so, at the beginning we were talking about how, you know, 10% of patients that are high-risk are getting referred for or getting Egds. And I mentioned that specifically with cancer, the low incidence of a previous endoscopy is really, really discerning when you are stressful because when you're taking out somebody's esophagus, and you look through their chart and you think, gosh, they've had, they're up to date on their colonoscopy. I wish someone would have done an upper endoscopy on them and they might not be in the situation today.

Amitabh Chak 1:24:23

OK.

Christy Dunst 1:24:27

And so I know that the negative predictive value is hugely important, but for me in my clinical practice, anything we can do to get these high-risk people to get an endoscopy, we should be doing it and we know all the risk factors for esophageal cancer and I strongly believe that nobody should be needing an esophagectomy for esophageal cancer in with today's technology and the things that we know.

This screening test will not only make people that have a negative test feel better and move on with their lives, but it will significantly improve our care of the of the high-risk patients. It's really important.

Amitabh Chak 1:25:04

Yes.

Gabriel Bien-Willner 1:25:17

Thank you, Doctor Iyer.

Prasad G. Iyer 1:25:21

Yes, thank you. I think that's a great point to emphasize and recognize in my mind what we are doing at the moment with endoscopy is unfortunately not been working due to all the barriers that we just talked about. This kind of a non-invasive office-based test really allows us to break that paradigm and put our arms around people.

There is also evidence to show that most endoscopies are done for symptomatic reasons and those patients have a very, very low prevalence of parents. But what this kind of test will do is that it will.

Amitabh Chak 1:26:06

OK.

Prasad G. Iyer 1:26:10

Increase the yield of that endoscopy and we know the resources for endoscopy are limited as it is. There's a problem with access. So, to me that's a great point that needs to be emphasized and hopefully recognized.

Thank you.

Gabriel Bien-Willner 1:26:29

Thank you, Doctor Glover.

Jamie Glover 1:26:31

So, I told you how I use this test as a rule out test based on the numbers and the data but what my rule in test is, is actually the risk factors like it's the symptomatic or a treated GERD and everything else. So, like the patients have already been ruled in. So, I guess, I don't really understand why you're using the word ruling test. I just want to just throw that out there. But maybe a ruling test exists somewhere, but we already ruled the patient into needing something, you know? So, I, you know, I just think of this as a rule out test, what we're talking about here today, so.

Gabriel Bien-Willlner 1:27:08

No, thank you. You're right to question but understand that we sometimes we want things stated very plainly through subject matter expertise and that's why you may. I'm not telling you that's exactly why this is here, but when you have a test that has a yes or no answer, it's good to understand the implications.

As to what it what its intended use is and what its intended use could be. And in this case the question could be, does this when positive change your yeah.

Jamie Glover 1:27:40

Yeah, so positive still tells me to do what I was gonna do anyway but now allows the patient to be adherent to that.

Gabriel Bien-Willner 1:27:49

Great. Thank you, Dr. Chak.

Amitabh Chak 1:27:53

Yeah, what I was going to say is the rule out test is the non-endoscopic test. The rule in test I would argue is the endoscopy and this test gets more people to get the endoscopy. So, you can do your rule in test because that's the test that 100% determines whether you have or not. So, it's a combination of strategies. That's what I think brings clarity.

Gabriel Bien-Willner 1:28:22

Great. Thank you very much, Doctor Smith.

Michael S. Smith 1:28:24

100% agree the non-endoscopic screening is a rule out test that enriches the yield of the rule in endoscopy test. That's exactly right. Totally agree with Doctor Chad.

GABRIEL BIEN-WILLNER 1:28:35

Can I make a comment? I just want you guys to sort of respond to whether it would be appropriate to consider these kinds of services, kind of like a triage for endoscopy.

Amitabh Chak 1:28:55

Yeah, exactly right.

Gabriel Bien-Willner 1:28:57

Doctor Shaheen.

Nicholas J Shaheen 1:28:59

I don't know if I would phrase it as a triage per SE, although certainly you are using this as a stoplight as to whether or not you're going to go. I think that it's a fundamental change in the care pathway because 75 plus percent of patients are taking the off ramp based on the on.

Amitabh Chak 1:29:10

Cool.

Nicholas J Shaheen 1:29:18

This test allows us to really change the way that we think about it. I mean, right now we all sit and moan about the fact that 10% of people that need the test get it. If they actually showed up, we couldn't take care of them anyway because we don't have. We have access issues as I think Prasad or somebody said. So, the fact that we could stick this in front of it allows us to get the people that need the test getting the test. So, I think that in some respects you're right, but I think it's a more fundamental change.

Gabriel Bien-Willner 1:29:55

Thank you, Doctor Smith.

Michael S Smith 1:29:58

Yeah, I would agree with Doctor Shaheen. I mean, I think to me the triage, the suggestion of the word triage is that you're still in A Gray zone. You could still go either way. Maybe it gives you a hint one way or another. I think this is what we're talking about with the characteristics we're talking about is really definitive test and it goes beyond what a traditional triage would allow you to do. So, it's triage plus.

GABRIEL BIEN-WILLNER 1:30:19

Understood at Doctor Glover.

Jamie Glover 1:30:24

So, not very many years ago, colon cancer screening guidelines changed to starting colonoscopy at 45 for those who choose colonoscopy for that. And that overloaded our local GIS for a while. So, I just wanted to make a point that me as a primary care doctor referring to a GI who would be the one to do the EGD.

As the ruling test, you know, there were access issues, and I think they're a little better than they were. You know, it's been a few years, but there are definitely access issues. You can't. There's not enough endoscopist, endoscopy suites, I think to do all the endoscopies. So, in that way, yeah, it's kind of a triage test, but it's still just a ruling.

Gabriel Bien-Willner 1:31:04

Thank you, Doctor Panzarella

Paul S Panzarella 1:31:06

Yes. Also, to add a little bit more to that, in our practice we essentially screen every new patient that walks into the door. I have three partners and just to give you an idea of sheer volume, we have a very busy surgery Center in between myself and three partners, we average anywhere between 7 to 800 cases per month. So, you would imagine that we are obviously not scoping everybody we see but also speaks to the volume of patients that are coming through our doors who have the opportunity to fill out this questionnaire and enable us to identify who's the highest risk that would qualify for this test for sure.

Gabriel Bien-Willner 1:31:55

Thank you. We've got Doctor Loveless, who is a Medicare medical director with CGS who has a question. Go ahead, Meredith.

Meredith Loveless 1:32:06

Hey everyone, my question is, since it ties into what we're discussing, are there comparative studies that compare the test to EGD and if a policy had a limitation, so say for instance if there's a negative non-invasive test that would exclude being able to do an EGD. Would that be considered an acceptable limitation?

Gabriel Bien-Willner 1:32:35

Hey, Doctor Shaheen.

Nicholas J Shaheen 1:32:37

So thanks for the question. Terrific questions both. All of the literature use the EGD as the gold standard and then work the performance characteristics off of the EGD. So, they are all comparing EGD to the non-invasive test.

With respect to your second question, I think it'd be entirely appropriate to create guidance that says that if the test is negative that they should not go onto an upper endoscopy absent another new or different indication for endoscopy.

Why? You know, you shouldn't be ordering this test if you were planning on doing endoscopy afterwards regardless. So, I think that's the case. We just have to be careful about how it's worded, just in case a new or different symptom constellation comes up.

Gabriel Bien-Willner 1:33:24

Thank you, Dr. Smith.

Michael S. Smith 1:33:26

Yeah, I would like to echo what Doctor Shaheen said. I would not be in favor of a policy that sort of blanket said no more endoscopy if you get this because for those new symptoms and that does happen. Obviously patient histories are dynamic. We would not want to be stuck in a delay were trying to get approval and an exception to the policy ends up costing the patient time, which could be a very precious resource and save a lot of healthcare dollars and also a lot of quality of life for the patient.

Gabriel Bien-Willner 1:33:56

Thank you, Doctor Booth.

Adam Booth 1:34:00

Yeah, I would. I would also agree with the gastroenterologist and the surgeons on that as a pathologist, I would say, you know, I get a lot of biopsies for, you know, for GERD symptoms and it's EOE. So, imagine I'm not gonna, if I never get that biopsy, I'm not making that diagnosis, so, you would potentially exclude that patient from being covered for an EGD if they need it with those other symptoms, so.

Thanks.

Gabriel Bien-Willner 1:34:24

Understood. Thank you. I'm going to, in the interest of time, the rest of the questions are going to be fairly focused. Let's go with I think we've covered the meat of the testing specifically.

But can you guys clarify what is? And I know this is going to be one of those questions that's going to seem obvious, but I want it stated, what is the appropriate clinical setting for the performance of this test? So, we've got a lot of.

Gastroenterologist on this call. Are the gastroenterologists the ones that are going to be performing this test or is this being done by primary care and the family clinic or other locations? So, what are those other locations could be Doctor Glover?

Jamie Glover 1:35:12

OK. So, I think primary care office should be one of the appropriate settings because some patients logistically or anxiety reasons or whatever, just they just don't go to other places. They just want to come to their own doctor and that's about it. So, I think it needs to be done there as well as at maybe community GI.

And that could be done. You know, we weren't appropriately trained. There's a very clear training process in performing this procedure properly. And initially I didn't have the volume to have my nurse trained in that. I know we're talking about how we could get her the volume and potentially do that so we could administer ourselves.

But it worked very well to bring a nurse into the practice who was trained to do that. And I was actually in the procedures observing and so was my nurse, you know. And so, I think primary care needs to be one of the settings, appropriate settings where it is performed and it will improve adherence if that is one of the settings where it can be, you know, done properly with proper training.

Gabriel Bien-Willner 1:36:14

Thank you, Doctor Chak. But first, can I ask Meredith, can you put your hand down unless you have another question?

Thank you, Doctor Chak.

Amitabh Chak 1:36:24

Yeah, main advantage to point of care unsedated office-based test is that it can be done anywhere. If you have personnel who are trying to administer it, it's not a physician who has to administer it.

It can be done in firefighters, it can be done in primary care settings, it can be done at your local mall. But it allows you the flexibility and to reach where the patients are, especially in areas of endoscopy deserts where endoscopy services are not available, so you can identify the appropriate patients who need to be referred to an endoscopist.

Gabriel Bien-Willner 1:37:07

Thank you, Doctor Panzarella

Paul S. Panzarella 1:37:10

I think also to speak a little bit more about that is of course there is an ease of use of the test, but in my practice there is definitely an ease of performing the test. I myself learned how to do it and went through some training sessions and it's relatively simple to do. So, I offer this as something I can do for my patients throughout the month, but also in terms of a workflow, we set aside every 4th Wednesday as a dedicated screening day. So, my three partners are aware of this. So, when we're gathering questionnaires and seeing patients throughout the month, everybody knows what day that is, .and we try to schedule as many patients as possible.

And the team from EsoGuard sends nurses out to my office once a month and they perform the test for my patients. So we have our built-in schedule between, you know, me, my three partners and two nurse practitioners.

To have patients already on the schedule, but in addition having patients that are coming in real time that day, say for a screening colonoscopy and we identified that they have risk factors and we asked them one, have you been fasting and two, do you have two minutes? And that's essentially striking while the iron's hot to identify additional patients. So, it truly has worked out very well for our practice.

Gabriel Bien-Willner 1:38:53

Thank you, Dr. Dunst.

Christy Dunst 1:38:56

Yeah. So as was mentioned, the test can be done in the mall. It can be done everywhere as long as we have the appropriate training, which is A really short learning curve that the company is really helpful with.

Amitabh Chak 1:39:12

OK.

Christy Dunst 1:39:12

So in Orange County, we've identified that primary care physicians or primary care offices are a good target as well as general GI practices, specifically general GI that has motility testing in their office already because their staff is really great at performing the tests and doesn't require any additional education. We have been rolling it out to the primary care offices and providing education and support and some of them are going to incorporate it and for the ones that don't want to for whatever reasons. The main campus is holding screening days so that we can schedule the patients from all across the county to come to the one day and have their test. There's a lot of flexibility here and it's really pretty easy to roll out. It's very encouraging and a lot easier than scheduling all these endoscopies that we would want.

Gabriel Bien-Willner 1:40:18

Thank you, Doctor Smith. And I will tell you guys; we've got about 12 minutes left. So, Doctor Smith, you can comment or not depending on.

Michael S. Smith 1:40:26

Yeah, I want to provide a little real-world experience data behind the anecdotes that you just heard, right. Well, I'm a co-author on a study that's coming out soon. I'm sorry it's not in the peer-reviewed literature for in time for this meeting, but it was over 12,000 patients, over 96% success rate and completing this in real world settings, high patient satisfaction.

Gabriel Bien-Willner 1:40:29

Yeah.

Amitabh Chak 1:40:44

OK.

Michael S. Smith 1:40:45

Satisfaction and good performance, very strong performance characteristics for the testing. And those tests were done in A variety of places, everything that you've heard, PCP offices, GIS, surgeons, centralized lab settings. So, you know there is, we do have data Unfortunately, it's just not out quite yet.

Again, over 12,000 patients in this study were done in those different settings showing the flexibility of being able to perform A test like this in in multiple settings in order to maximize patient outreach and connection.

Amitabh Chak 1:41:13

It.

Gabriel Bien-Willner 1:41:18

Thank you. I I'd like for a brief response to the next question which is and I think this has been touched on already, but just you know a brief comment, have these tests demonstrated the ability to increase the number of BE and adenocarcinoma patients compared to other prior diagnostic techniques, meaning yes, we can rule out patients who now don't need endoscopy, but the implementation of whatever you don't want to call it triage, but the purification of likely true positives has that resulted in a net increase in in the identification of Barrett's esophagus patients. That's part one. And then also adenocarcinoma, I'd like some comment on more advanced disease if possible. And then the second part to this is it's also known that a good number of patients who get adenocarcinoma never had GERD symptoms. And so, I'd like some comment on what the realistic expectations for the increase of our yield identification of BE and more dysplastic or adenocarcinoma yield is going to be knowing that not everyone presents with some of the symptoms needed for the performance of this test. Doctor Shaheen.

Nicholas J Shaheen 1:42:50

There's actually some remarkably high-quality data originating out of the UK from a great research group over there led by Rebecca Fitzgerald. There's a study called the Best Three study that uses a non-endoscopic screening method. In this case it was not ESA check, it was actually Site a sponge, not a balloon, but similar idea taking patients with a constellation of risk factors, randomizing them to offering the test versus standard of care.

What they found was that there was a ten-fold increase in the diagnosis of Barrett's esophagus just by offering them the test. I'm not saying that we aren't comparing just the ones that went through. Just by offering them test, you find 10 times more Barrett's. That study also found multiple adenocarcinomas. So, I think that.

The short answer to your question is yes, there are good data to show that the incorporation of a non-endoscopic test does increase the number of cases you find. As to your second question, you're right, 40% of the cancers occur in people without reflux. Right now, we're getting 10% of the cancers of the people with reflux, which is why we're not changing anything. I would be delighted to find half the cancers in the people with reflux. It would make an enormous change. It was who? Was it Paul's analogy of a basketball stadium? Imagine 1/3 of the basketball stadium being saved.

I want to be one of those seats. You know, I think it makes a lot of difference.

Gabriel Bien-Willner 1:44:27

OK, we're down to just 8 minutes. So, I would say I will ask Doctor Wani to keep it brief.

Sachin Wani 1:44:34

Oh, I was just going to add that, you know, let's also recognize what an achievable endpoint is, right? To create or design a trial where you're actually comparing screening using this strategy versus no screening and using the endpoint of esophageal cancer, but you ask is not realistic. This is not a cancer that's as common as some of the other cancers that we've talked about. So that's just an important thing to bear in mind. And as Nick pointed out, we've got RCT data showing that you increase the diagnosis of Barrett's.

Gabriel Bien-Willner 1:45:08

Thank you, Doctor Iyer.

Prasad G. Iyer 1:45:11

I'll keep it brief. I think we should not let perfect be the enemy of the good. I think we need to start somewhere, and we are so far down on our spectrum of screening that any improvement, as Nick said, is a worthwhile improvement.

For us, we can always broaden those criteria down the road, but I think the reflux plus the risk factors is a great starting point at this time.

Amitabh Chak 1:45:41

Thank you and Doctor Smith.

Michael S. Smith 1:45:44

Yeah, just I very briefly agree with the comments. I would say that the best three data that Doctor Shaheen mentioned I think is generalizable to non-endoscopic screening in this disease state. And I would argue the performance characteristics of EsoGuard are better than cytosponge in the literature. So, in all likelihood it probably would find even more disease than what they were showing in that trial.

Gabriel Bien-Willner 1:46:05

I'd like to follow up with Doctor Shaheen on and anyone else on best three had a very specific question there. UK has an obviously very different health system than we do and one of the reasons in in reading that the series of studies best 1-2 and 3 was that they had a crunch on availability of access to EGD in a way that is just perhaps different than what we observe here in the United States, and they needed to have an alternative. That's my reading of that work, which led them to develop this test and led to the best three clinical trials. The question is the best three data really relatable to the US Medicare population? Is there information in there that really is a reliable result that could be supposed on the US population, or should there be great care taken in the clinical utility results of that best three trial?

Nicholas J Shaheen 1:47:15

Yeah, I would agree that these are different healthcare systems. However, when you think about the things that could screw up that trial i.e., is the distribution of the risk factors different? Is the prognosis different for Barrett's over there? Is what they called Barrett's in the trial different over there? The answer is to all that stuff is no. So, you know, I do think that it's extrapolatable to the US population, although you're right, it's a different system. But the important stuff like, you know, what's the prevalence of Barrett's in the at-risk population? What's the distribution of risk factors? How do the tests perform? All seem to be similar, so I think where the rubber meets the road, we're probably fine in generalizing that that result.

Gabriel Bien-Willner 1:48:05

Thank you, Doctor Iyer.

Prasad G. Iyer 1:48:07

Yeah, similar points. You know, another similarity I would say is, you know, the test positivity rate for instance, the criteria that they are actually using to select those patients are very similar to our criteria and I do feel that the results are translatable. I would certainly say that while we know that the National Health system is a different system, I do feel that access to endoscopy is not really uniform across the United States, particularly in areas where prevalence of Barett's may actually be higher. So, I think we have to be careful to perhaps not say that we do better off in terms of endoscopy. We, I think, have similar challenges to access to endoscopy that they have as well.

Gabriel Bien-Willner 1:48:58

Thank you. I'm going to move on to another question. I know this has been touched on, but I want it kind of explicitly stated. Do you have any concerns for the use of these kinds of tests as part of a Barrett's esophagus workup knowing that these services or these tests don't evaluate for other kinds of GEJ pathologies.

Amitabh Chak 1:49:23

OK.

Gabriel Bien-Willner 1:49:23

Doctor Smith.

Michael S. Smith 1:49:24

None, because again, it goes back to the conversation we had earlier about red flag symptoms and other indications for endoscopy that would put you in a totally different management pathway for the patient. So, you know, if we're talking about a GERD patient with no red flags where you're considering it again because they have the symptoms and they have the demographics that meet the societal guidelines for screening. It's one thing, but other disease, you know we talked about eosinophilic esophagitis for example came up earlier. If that patient has dysphasia or weight loss or failure to thrive in one way or another, the screening the high-risk screening for Barrett's piece is irrelevant. You're going to provide the standard of care for the patient based on the clinical presentation, which would be different in this case and I think that's again as long as you have that clear piece that we talked about in terms of the exclusion criteria for when an endoscopy would be allowed we have to realize the patients presenting symptoms may be dynamic. The history may change history is history and very subjective and patients aren't always consistent historians. If they present additional data, we may change how we manage that patient and we have to be able to maintain that. But I think you know there's no concern at all for a patient who's. with their presentation and it's just reflux only with a concern for could they have Barrett's?

Gabriel Bien-Willner 1:50:47

Thank you. I'm going to skip another question. Does the evidence support the accuracy of these tests in long segment disease, short segment disease, or both? Does it matter for test selection? Does it matter for the clinical value of the service?

Amitabh Chak 1:50:49

OK.

Nicholas J Shaheen 1:51:09

The second part's easier than the first part. Yes, it matters. The long segment disease is more dangerous than short segment disease. If you ask me what I would want to miss the least, it would be long segment disease. The good news is that at least in the data that we have to date and it appears that there's no differences in detection rates even amongst short segment disease. Although I tell you long segment disease is the most dangerous, there's a bit of a catch 22 because the vast majority of disease is actually short segment disease and we don't want to miss that disease even though it's of lower risk.

So the fact that that it's got high sensitivity for both kinds of disease is actually a very important feature of and needs to be a feature of any test that's going to sit this way in the pathway.

Gabriel Bien-Willner 1:51:57

Thank you, Doctor Glover.

Jamie Glover 1:52:00

OK. So, it sounds like the answer was both, but I just wanted to point out that my patient Dan who had short segment disease, not that that's like some great numbers, but it's just a little clinical contact. No, he has short segment cancer, not short segment Barrett's esophagus, but It picked up at least positive and I was able to get that patient compliant and going on to the ruling test which was EGD.

Gabriel Bien-Willner 1:52:25

Thank you, Doctor Chak.

Amitabh Chak 1:52:28

Yeah, Nick caught up when he said short segment is not as risky, but there's more of it. So, for cancer, you want all. So yeah, you want the whole spectrum.

Gabriel Bien-Willner 1:52:41

Thank you, Doctor Smith.

Michael S. Smith 1:52:42

Yeah, agree with that. And you know EsoGuard sensitivity for short segment disease is 90%. So very impressive numbers. And we know again that 70% of the target population that we're looking

at has short segment disease. So, the performance here is important for short segments for all the reasons that have been outlined before.

Gabriel Bien-Willner 1:53:02

Thank you. I'm going to finish up with one last question. Hope you guys have another couple minutes here. Do you guys have any concerns with these tests for accuracy in detecting low versus high grade dysplasia? We talked a lot about Barrett's esophagus, but I want to move into dysplasia if that's OK.

Doctor Gibson.

Joanna Gibson 1:53:28

I mean, I'd love to hear others, but my sense is that pathology is going to continue to be the gold standard for diagnosing low- and high-grade dysplasia And so, I think if you end up with a positive screening test with this non-invasive approach, you're going to go for endoscopy and confirm whatever pathology they're having to be.

Gabrie Bien-Willner 1:53:49

I think that presumes, however, that the test is positive when there's any pathology and then you can decipher what that pathology is. I think the question is really performance on the test that's many of these tests are geared to or developed to detect Barrett's esophagus and because dysplasia and adenocarcinoma are just less frequent that they may not have as much data or may not be as accurate once there is dysplasia and that's really what I'm trying to understand is how concerning is that? Or you know, am I off base and these tests are just graded everything.

Doctor Booth.

Adam Booth 1:54:28

Yeah, I don't think this test would be a replacement for determining low grade or high-grade dysplasia I mean, admittedly as GI pathologist, we struggle with that to begin with. But I wouldn't, I wouldn't say that this test would be a replacement for that. And just like Doctor Gibson said, BIOS itself is, you know, gold standard.

And that is diagnosis.

Gabriel Bien-Willner 1:54:50

Sorry, Doctor Smith, I skipped you. I'm coming back to you.

Michael S. Smith 1:54:52

That that's OK. I would just say that you know the data is really good across the spectrum of disease and dysplasia, 100% sensitivity for esophageal adenocarcinoma It's very good for dysplasia as well as non-dysplastic disease. So, I have no concerns about this, and I would agree that gold standard, the standard of care if the screening test.

Michael S. Smith 1:55:12

The high-risk screening test is positive is a high-quality endoscopic examination with targeted biopsies of focal lesions and random biopsies of general disease that doesn't have any distinguishing characteristics. And as long as people are following that, that's where we're really looking at coming up with the dysplasia grade and looking for nodularity, ulcerations, other abnormalities that will target you to the sites that will be highest risk for advanced neoplastic disease.

Gabriel Bien-Willner 1:55:40

Thank you. Let's go, Doctor Meltzer.

Stephen J. Meltzer 1:55:43

Yeah, I would just echo what Doctor Smith and the others have said and just point out that many of these tests are based on DNA methylation and all the ones with DNA methylation are higher levels of methylation and greater frequency of methylation in as you go up the spectrum from metaplasia to low and high and adenocarcinoma So, they're actually quite they tend to be more sensitive as you go up in neoplasia grade.

Gabriel Bien-Willner 1:56:14

Thank you and Doctor Chak.

Amitabh Chak 1:56:17

I'd say going back to the earlier discussion at the big picture level, it's still a rule out test and the low grade, high grade cancer, et cetera comes at the rule in test at the endoscopy at a high negative predictive value.

Rule out test that gets people to get upper endoscopy will find you the dysplasia as the short segments, the high long segments and the cancer. So, at the big picture level it's detecting those Barret's that are not being detected getting people to get the appropriate high-risk people to come to upper endoscopy is testing it you know getting the whole spectrum is just an added bonus, but the primary thing is still the rule out test

Stephen J. Meltzer 1:57:01

Check.

Gabriel Bien-Willner 1:57:05

OK. Well, thank you very much. I think we've used up all of our time. I want to thank all the participants. We had a lot of them, but we got really great perspectives from everybody. This has been a very pleasant experience. Thank you guys so much for sharing your knowledge with us.

And this will greatly impact our ability to move forward with writing policy or considering that reconsideration request on the existing policy. So, with that we're going to end the meeting here. I know that there's there are some questions we didn't directly discuss, but we kind of danced around all the information, I think that was in all of these questions. I appreciate everyone's participation and everyone who called in. We had I think at some more than 200 people who called into this. So, thank you all very much for your participation and looking forward to talking to you all again someday.

Take care of everybody.

Paul S Panzarella 1:57:57

Thank you.