Anthem, Inc.
Moderator: Dr. Ola Awodele
4/11/2019
3:00 p.m. eastern time (ET)

Operator: This is conference # 2881218.

Operator: Ladies and gentlemen, thank you for standing by. And welcome to the OVA1 and Other Multi-Marker Serum Tests Related to Ovarian Cancer Testing. At this time, all participant lines are in a listen-only mode.

Throughout the call we will be conducting a question and answer session after each presentation. To ask a question via the phone, please press star, then the number one on your telephone keypad. To withdraw your question, press the pound key. Thank you.

At this time, I would now like to turn the conference over to Dr. Awodele. The floor is yours.

Ola Awodele: Thank you very much, Jamaria. Good afternoon and I'd like to welcome everyone to this contractor advisor committee meeting, a.k.a. CAC. The purpose of our call today is to obtain advice from our CAC members about the strength of the published evidence on use of the OVA1 and other multi-marker serum tests related to ovarian cancer testing and assessing malignancy risk adnexal masses in women with planned surgery.

In addition to the discussion, the CAC members will vote on predistributed questions. All speakers must have completed and returned the disclosure statement prior to today's call. The meeting is also open to the public as observers.

Well, as we all know, due to the nature of the topic that we have today, the specialties involved are prone or there's an increased possibility of emergencies and such has happened today. So there are some people who had requested or had turned in – had indicated that they would be on the call, but their schedules today – emergencies have not permitted everyone to attend. So I just wanted to let everyone on the call know that. OK.

NGS does currently have OVA1 as a noncoverage service in our LCD L33629. And we received a valid reconsideration request from Vermillion which we are responding to in accordance with the *Program Integrity Manual*, 100-08, Internet-Only Manual Chapter 13, Section 13.3.3.

Before I go any further, I just wanted to give a quick review of the topic. So cancer of the ovary, fallopian tubes and peritoneum is staged surgically and the prognosis of ovarian cancer is closely related to the stage of the tumor at the time of diagnosis.

If malignancy is detected while still localized in the ovary, the estimated five-year survival rate has been found to be about 92.5 percent. Conversely, five-year survival rates among women diagnosed with advanced stage ovarian range from 20 percent to 40 percent.

Overall, early-stage diagnosis is correlated with higher five-year survival rate, establishing a need for early detection and intervention. Treatment options for ovarian cancer can vary. However, surgical intervention is commonly used to establish staging and disease confirmation.

Currently, NCCN guidelines, together with ACOG and SGO guidelines recommend that a woman with ovarian cancer should undergo surgery by a gynecological oncologist. However, it's estimated that about 33 percent to 60 percent of patients with ovarian cancer are treated by a gynecologist/oncologist that is according Eskander et al, 2016 and the NCCN in 2017.

Four overall outcomes for ovarian cancer can be partially attributed to the asymptomatic nature of the disease. One potential identified feature of ovarian cancer is the presence of an adnexal mass, a growth in the tissue and the adnexa of the uterus, which refers to a mass in the ovary, fallopian tube or surrounding connective tissues.

Estimates suggest that about 90 percent of all adnexal masses detected in premenopausal women and up to 60 percent of masses found in post-menopausal women are benign. However, the presence of an adnexal mass does carry a risk of malignancy.

Initial diagnosis of adnexal masses relies on a variety of diagnostic modalities. This includes clinical examination, ultrasound assessment and more recently, tumor biomarker levels have been included according to Abdalla et al in 2016 and Anton et al, in 2012.

So reliable screening tools that assess the risk of ovarian cancer for women who present with adnexal masses are paramount in providing optimum health care recommendations for patients including referrals to gynecology/oncology when appropriate. This is according to Euland, Ware Miller and Tall which we'll discuss a little bit later.

Since we're here to discuss the literature or the literature that is surrounding these class of tests, I have sent out to our CAC members an annotated bibliography to help with this discussion today. Prior to going into this discussion, I would like to give Vermillion, our requester, an opportunity to present and they have been informed that they could speak on the clinical utility of the test.

Dr. Elizabeth Cherot was submitted as the person who would speak on their behalf today and we will start off today's meeting with Dr. Cherot presenting. So, operator, if Dr. Cherot is on the line, you can unmute her line. And also, I just wanted to let our CAC members know that Dr. Cherot has about five minutes.

I've been informed by Mr. Yeager that Dr. Schulman will just speak for one minute to two minutes on his clinical experience and, after that, if there are any questions for them from the CAC members, you can just indicate as the operator would tell you

how to do and we can ask them all these questions before we move on to the next speaker. Thank you. Jamaria, did we have Dr. Cherot?

Ola Awodele: Is this Dr. Cherot?

Elizabeth Cherot: This is Dr. Cherot. Can you hear me?

Ola Awodele: Yes, I can hear you.

Elizabeth Cherot: Perfect. So I'm assuming everybody else can. Thank you for allowing me to address the committee for the use of OVA1 for women with adnexal masses. It's an – I just want to let you know I'm – my background is that I'm a generalist, so I'm an OBGYN. I've been in practice for about – almost 20 years.

Ola Awodele: Sorry, Dr.Cherot. OK. Could you also include your conflicts of interest, if any?

Elizabeth Cherot: There's none. I'm a generalist who uses OVA1, but has no financial stake, background or anything with Vermillion, if that helps. So…

Ola Awodele: Yes.

Elizabeth Cherot: Yes. So I was asked because, honestly – and I guess I'll start with my clinical case. I had a couple of years ago a woman with an adnexal mass in her '60s who never complained of anything. And, you know, I only had seen her for annual exams; came in; did an exam; I didn't feel anything. I sent her for ultrasound. She had a mass.

It wasn't really diagnostic for anything that was cancerous and the short speech here is that OVA1 was positive. And I didn't have a GYN oncologist to refer to in my own institution. I had to send her out and, you know, God forbid, I had taken her to the OR myself would have found cancer and would not have been able to take care of her properly.

So I did send it out and actually diagnosed a stage one cancer which, honestly, in my 19 years, is really unheard of. We usually always see them in the third stage. So if an adnexal mass is discovered in a woman of biopsy really is contraindicated because as most of, I assume, people on the phone know that the tumor will spill into the abdomen and that increases stage.

So physician assessment and imaging studies, really ultrasound, are helpful. But a large number of patients with adnexal masses benefit from the use of tumor markers to help decide if malignancy is a risk and if referral to gynecologic oncologist is necessary.

So I want to point out that CA125 is indicated for use as an aid in the detection of residual or recurrent ovarian carcinoma and for use in monitoring patients for disease progress or response to therapy.

OVA1 is indicated for women who are over the age of 18, have an adnexal mass present for which surgery appears planned, but you haven't yet referred to an oncologist. So the OVA1 test is an aid to further assess the likelihood that malignancy is present when the physician's independent clinical and biological evaluation doesn't – does not indicate malignancy.

The test is not intended as a screening or standalone diagnostic assay. So to speak to the publications, there's published data has shown that OVA1 has higher sensitivity in detecting ovarian malignancy than both CA125 and ROMA.

This is especially true in premenopausal women, where the majority of masses are found; and in pre- and post-menopausal women with early-stage disease just like the example I gave you today.

The ability to detect ovarian cancer when there are no other obvious signs of malignancy allows women with early-stage disease to be appropriately referred to the GYN oncologist and have a proper staging. OVA1 also detects non-epithelial cancers that CA125 does not.

There have been four publications independent of Vermillion that have shown that African-American women have lower CA125 levels in both the healthy state, high-risk patients and women with ovarian cancer.

Data recently presented at the American Association of Cancer Research and the Mid-Atlantic GYN/Onc Society highlights the lack of sensitivity of CA125 in this particular population. OVA1 has demonstrated superior sensitivity for detection of malignancy in the African-American population. So recent guidelines have been updated to include in favor OVA1 over CA125 or ROMA in evaluation preoperatively for women with adnexal masses.

The American College of OBGYN saw ACOG, which most of us follow as generalists, recently elevated OVA1 from noncoverage to a level B recommendation, which is a big move in the clinical management guidelines for OBGYNs for the evaluation and management of adnexal masses. So level B is the highest level recommendation possible for OVA1 as it's not indicated to replace the level A recommendation which is really ultrasound and physical exam.

So the guidance provided by ACOG represents that most relevant guideline to managing adnexal masses at onset and to use in determining medical policy in OVA1. Not only does it emphasize that OVA1 has demonstrated higher sensitivity and negative predictive value for ovarian malignancy when compared with clinical impression alone, but also emphasizes that, "CA125 measurement is less valuable in predicting cancer risk in premenopausal women than in post-menopausal women,".

So, UpToDate, which a lot of us go to, recently published a report on adnexal mass guidelines reiterating support for OVA1. The report references (in support) to the ACOG guidelines regarding referral to GYN/ONC for women proceeding with surgical evaluation of adnexal mass that is highly, you know, suspicious of ovarian cancer.

And they state that, given the available evidence, we suggest OVA1, Overa, or ROMA rather than CA125 to decide whether a patient who has planned for surgical evaluation for an adnexal mass should be referred to a GYN oncologist. Test availability and expense may factor in which test is most appropriate for each clinical situation.

So, as I said, you know, in the last seven years, I have used OVA1. I find it really allows me to refer patients appropriately to GYN oncologists and, honestly, let's me reassure myself that I properly manage patients with benign conditions.

Personally, I find that, preoperatively, if you're prepared for surgery, that that gets your patient the best outcome. They are great studies that it's not just who the surgeon is, but what the surgeon is and how they prep the patient for surgery.

So I found cases where ultrasound and CA125 and ROMA would have led me to believe that a patient on a benign condition and an elevated OVA1 determine the patient had early-stage ovarian cancer.

So I'm happy to answer any questions. I know other Medicare contractors have a positive coverage policy for OVA1 and a growing number of commercial insurers now cover OVA1. So, if I can turn this over – I think it's Dr. Schulman that's speaking next, so I can be muted. And then, I…

Ola Awodele: Yes.

Elizabeth Cherot: You good.

Ola Awodele: Yes. Thank you very much. If you can…

Elizabeth Cherot: I can stay on the line. I'm happy to stay on the line. I might have an emergency as I am on leave or in delivery today, but I will stay on the line as long as I can.

Ola Awodele: Just for a couple more minutes so Dr. Schulman can comment.

Elizabeth Cherot: Yes – no, absolutely.

Ola Awodele: We'll open it up to the public and to the CAC members if they have any question. Thank you very much. Jamaria, could you open Dr. Schulman's line next, please?

Operator: Press star one to open your line, star, and the number one.

Ola Awodele: I don't believe Dr. Schulman – OK, if he – if he is not on the line yet, because I don't see him on the line, could we ask the CAC members if they have any questions for Dr. Cherot, so please ask them now.

Female: I think Dr. Schulman just text me that they're on the line.

Lee Schulman: Yes.

Female: There you are.

Ola Awodele: Perfect.

Lee Schulman: Hello.

Ola Awodele: Thank you.

Lee Schulman: OK. Good afternoon, everybody. Everyone can hear me?

Ola Awodele: Yes. I can hear you.

Lee Schulman: OK. So my name is – my name is Lee Schulman. I'm a professor of obstetrics and gynecology at Northwestern University in Chicago. I am an OBGYN geneticist and

part of my research and clinical responsibilities is to run the ovarian cancer early detection program in Chicago here.

And it turns out to be one that probably is the largest ovarian cancer early detection program with over 4,700 women participating mostly as a result of inherited mutations that predispose of ovarian cancer, but also because of family history.

I know you would want to know about disclosures. I – as opposed to the speaker, I am a consultant for Vermillion and have received compensation for consulting, but receiving obviously no compensation or any monies for today.

I think she gave a wonderful overview. I can't further emphasize the critical importance of an effective triage for women with an adnexal mass. Even in a high-risk population that I serve here in Chicago and really throughout the Midwest and around the United States, the ability to provide that information despite having a large GYN oncology service readily available makes for an incredible difference in the quality of care that women receives.

Our GYN oncologist, much like the rest of our services, are very busy. And clearly, one of the issues here is not to clog up the GYN oncology service with benign cases nor to have women who ultimately have cancer to be cared for surgically by general OBGYN surgeons who do not have the expertise for optimal staging at the initial point.

I think it's incredibly important to understand that, still in the United States, all too many women are being taken to an operating room without triage are being evaluated surgically found to have an ovarian malignancy. And then, because the surgeons don't have the requisite skill to continue, the staging are closed up and then sent off for GYN oncology assessment that usually happens four to six weeks later.

If it's been evaluated in this way that just that particular act reduces that woman's expected – or life expectancy by up to 25 percent. So if we are truly going to be able to optimize the care, not just the high-risk women that I see, but all women who present with an adnexal mass and that's about 300,000 women in the United States each year.

We have been without an effective triage approach. Ultrasounds detect the adnexal masses for the most part. CA125, as you heard, has only been approved for the evaluation of women with ovarian cancer to monitor recurrence.

It has been used because there has been nothing else. And it's clear that every professional society knows and discourages the use of CA125 just because it's a nonspecific assay that is found to be positive in a lot of women with benign disease. Yes?

Ola Awodele: Dr. – OK. If you can just wrap it up in about 30 seconds?

Lee Schulman: Sure. Again, as I said earlier, I can't emphasize the importance of OVA1 and this algorithm. It's been shown to be equal to or better than the other algorithms that are there and it truly helps to improve clinical outcomes for women with cancer, as well as women without cancer.

Ola Awodele: OK. Thank you very, very much. So, operator, could we find out if anybody – any of our CAC members on the line – on the participant line have any questions of either Dr. Cherot or Dr. Schulman?

Operator: Again, in order to ask a question, press star, then the number one on your telephone keypad. That's star and the number one. And your first question comes from Robert Babkowski.

(Robert Babkowski): Yes. Hi. It's Dr. Babkowski. I'm the chief of pathology and the lab training medical director here at Stamford Health Systems. We have an active OBGYN program – GYN oncology program. And the question really is for both Dr. Cherot and Dr. Schulman.

The data, clearly the CA125 is not a good biological marker for African-American women. It's clearly a – (I don't like) that – you know because there's just too many – there's too many false elevations and too many false depressions and I just – it's not a good marker. I think we all know that.

The real issue is the population that we would be applying this to and the utility of OVA1 in the premenopausal and the post-menopausal setting. Can we talk more about those two populations? Because I – well, do you believe that OVA1 is as effective in the post-menopausal adnexal mass group as it is in the premenopausal folks? I'll take either one or both of you.

Ola Awodele: So, Dr. Schulman, Dr. Cherot, could either of you speak to that or…

Elizabeth Cherot: So I'm not sure Dr. Schulman is still on the line.

Lee Schulman: Hello?

Elizabeth Cherot: Perfect. Go ahead, Dr. Schulman.

Lee Schulman: OK. So thank you for your question. The answer is you're dealing with two very separate demographics. And the reality is, is that this triage is specifically for women with an adnexal mass. It is not a screening assay and it's specifically not a screening assay.

So you are talking about, again, the 300,000 or so women in the United States that present with an adnexal mass. It's not for women with BRCA mutations. It's not for women with a fibroid uterus. It's an adnexal mass.

And we have shown – and it's not just we have shown – it has been shown that OVA1 provides a far greater positive predictive value and negative predictive value, first of all, in CA125 and also better than the – somewhat better than the ROMA algorithm as well. So not only does it provide value clearly for the premenopausal population who have the most number of adnexal masses.

It also provides important information for the post-menopausal population because, while their risk of cancer is increased – post-menopausal women with adnexal mass has a higher likelihood that that adnexal mass is malignancy – it again proves valuable to know whether or not that woman can be operated on in a secondary or community-based hospital with a skilled gynecologic surgeon or whether or not she

is best cared for in a – in an oncological surgical center with GYN oncologists and surgical oncologists.

So the value of OVA1 has been shown both in premenopause and post-menopause, is the value somewhat better one than the other? It's probably a little better than the premenopause, but the reality is, is that, whether we are talking premenopause or post-menopause, it is profoundly better than CA125 in either of those populations.

Elizabeth Cherot: I guess I would just – I would just add that it – you know, the OVA1 definitely has demonstrated the superior sensitivity in the African-America population specifically.

Ola Awodele: OK. Thank you very much. Any other question out there, operator? I don't see anybody in the queue. OK. Well, thank you…

Larry Clark: I have one more coming off the leader line Larry Clark. I'm one of the medical directors. And I just wanted to ask Dr. Cherot because I'm not sure what the differential diagnosis is. But in your particular patients who you said was in her 60s …

Elizabeth Cherot: Yes.

Larry Clark: You're not talking about the more advanced age of a woman in the reproductive range who had undergone, let's say, ovarian hyperstimulation. You clearly have a woman who is post-menopausal with the presentation of an adnexal mass.

How did you treat that? I mean, what is the differential beyond the strong presumption of neoplasm of one of the different types of ovarian cancer? And why would you not treat every woman of that age group? You know, we're asked to …

Elizabeth Cherot: So great question.

Larry Clark: Medicare bene, so what's the advantage to the Medicare bene?

Elizabeth Cherot: No, great question. So this is a patient who actually have – you know, had no family history; came in. Somebody who I really only saw for annual exams, did not – it's not somebody who I took very – took her pain kind of seriously, brought her in, did an exam.

I didn't feel anything on her exam. I guess – I'm in New Jersey, so average weight for New Jersey of BMI in her mid-30s. And I would love to tell you my clinical exam of 19 years that I could pick up a 4-centimeter mass.

So, yes, did her ultrasound as dutifully as any obstetrician would and chose not to send the CA125, but chose to send the OVA1. The bigger issue here is there was no ascites. I mean, I would love to tell you that I – I'm really good.

I think that the OVA1 pushed me to – absolutely pushed me to say I'm not going to take this out. I'm not going to have a back-up oncologist on standby, which I didn't even have in my institution at the time because we were in between GYN oncologists.

So I really needed to know did I need to take her, did somebody else need to take her. I wasn't really worried about torsion. You're absolutely right. In a – in a post-menopausal woman with a 4-centimeter cyst I should be suspicious.

I'm suspicious all the time. I would love to be able to – because, right, because it's deadly and had I said to her, "Why don't you come her in three more weeks, then we'll see if it's worse," to be – frankly, I thought I was thinking maybe appendix et cetera.

And again, pelvic pain in a 60-year-woman is not something that usually walks into my office. So, you know, could that cyst have been there for a very long time? I have multiple women who have cyst that I can quickly say, "Listen, this looks not suspicious, right," no calcifications on the ultrasound.

And by doing – there's no indication to do a CA125, right. There's really an indication to do the OVA1. So – and that would determine – and, honestly, if her pain – I might have said this is really maybe GI. Maybe this ovarian cyst had been there for years. I just happen to have caught it today.

Larry Clark: Please – so would you (please) explain that (sense) you said was "I felt the need to do the OVA1" and you made a discrimination from the CA125.

Elizabeth Cherot: Right.

Larry Clark: What made you choose this test over the standard marker? Bad or good-pathologist.

Elizabeth Cherot: But the standard marker, right, is indicated for the use – it – really for residual disease after the patient has been diagnosed. You know, because of the – what's out there in the lay public, many people come in and say, "I want a CA125 without an adnexal mass, without anything."

And what I'm really trying to do is diagnose somebody with better sensitivity and specificity with cancer. And preoperatively I thought, well, OK, could this have been either just acyst adenoma for the pathologist that's out there, this benign cyst that I could take to the OR as a generalist feel very comfortable that she's getting the right care.

My choice was to do something that would made a difference in her care and her management. And I had to have this patient drive a – believe it or not in New Jersey it was – you know, it's a whole another hospital and whole another system which my hospital would hate me for saying, granted 20 miles up the road doesn't seem very far. But for this particular patient without her standard doctor it was a difference.

The difference to do it was because I wanted to know, could I take this patient to the OR or was this something that an oncologist should really be taking care of?

And this woman, obviously, was an oncologist that really needed to be done. And really it's because of the sensitivity and specificity that I'm trying to do the higher sensitivity in detecting ovarian malignancy. And that has been proven above CA125 and ROMA. All right.

Larry Clark: Thank you.

Elizabeth Cherot: Yes, you're welcome.

Ola Awodele: Thank you, Dr. Clark. Any other questions?

Operator: At this time, I'm seeing there are no other questions in queue.

Ola Awodele: OK. Thank you very much, Dr. Cherot and Dr. Schulman. Thank you very much.

Elizabeth Cherot: My pleasure. Have a good day.

Ola Awodele: Thank you. You too. Operator, could you open up Dr. Zhang's line? Dr. Zhang will introduce himself, tell us a little bit about himself and any disclosures. He did fill out a conflict of interest paper prior to today, but I just wanted to indicate that Dr. Zhang is – has been invited to the call today to discuss the analytical validity.

He is someone that I came across while reading the article and found out that he is from Johns Hopkins University and actually had been involved in the actual discovery of the test. So I reached out to him to speak to us –to speak to us at the CAC about the analytical and clinical validity of OVA1. But since that's the main one that is being reconsidered, but yes, that's (about it). So if you could open Dr. Zhang's line.

Zhang: Hello? Can you hear me?

Operator: His line is open.

Zhang: Yes. Can you hear me?

Ola Awodele: Yes. We can – I can hear you, Dr. Zhang. Thank you for coming. You may begin.

Zhang: Sure. OK. First, I need to do a disclosure and a disclaimer and (why is the) OVA1 and also a second-generation product, Overa, was developed that partially supported by a sponsored research agreement to the Vermillion company and the Johns Hopkins University which we (have seen) about two years ago.

And the other thing is both OVA1, Overa were licensed to Vermillion by Johns Hopkins University and, since I'm one of the developers (I'm entitled to royalty payments), but I still keep my Johns Hopkins job.

So the other one is I'm currently also involved from as statistical consultant of Vermillion, for new product development and don't have anything to do with the OVA1 marketing or operation essentially ten years ago.

So also, I – because of that, I do not have direct knowledge currently, so the usage of OVA1 in the clinic. The description and some of the opinion said today is going to be what is the best (to my) knowledge and also memory of (some of that) since that's quite a while ago. And also, as a rule individual (scientist) with firsthand knowledge, so it's not the position of Johns Hopkins University (essentially) required to say that.

Then, come down to that why is (when it's developed) that we have several market center studies that essentially the biomarkers used in the OVA1 was discovered through a multinational studies by 350 patients from five institutions, actually from

Netherlands, Duke, from Royal Hospital for Women in Sydney and MD Anderson and Johns Hopkins University. Also stated in the discovery process.

Now, after that, we have several papers and one of the decisions to go through the development of OVA1 is actually they have 1,800 samples from six medical institutions across the world. And we use one of the center data that – to essentially mathematically derive the algorithm and that is not OVA1, just when we first started when we were trying to do that whether it's going to work from one particular institution and test on our five institutions and that's altogether by 1,800 samples.

And it has a very consistent separation from one institution to another to another. That gave essentially the green light for the company, Vermillion at that time has actually is not named (it's different) to commit their resource and funding for the actual development and eventual clinical trial for that.

(Part of the things I want to say) that which is very relevant to today's discussion is, when you have a test like that, typically people talk still. But actually, there is always one particular operating point how the test is going to be used. So essentially, where do you choose your cutoff point?

They're going to give you the sensitivity and specificity and also the corresponding predictive values, both negative and positive predictive values. That's for the OVA1 when we – was looking at it we used four criteria.

One is what is the size of the test population? For OVA1 is relatively small. And what is the prevalence of the trends in the (predictive) test population for OVA1 since that's for woman with adnexal mass and the decision to have surgery more or less is made because of a perceived risk of ovarian cancer?

So the prevalence is – from the two studies we have is about 20 percent to 30 percent, so it's relatively high. And then, the consequence of false negative, it is significant because ovarian cancer is a very deadly disease. But since the decision to have surgery is already done, the (same) question is who is going to do the surgery. So it is significant, but it's not as bad as just totally (miss) altogether.

On the other hand, the false positive – the consequence of false positive is that is actually relatively insignificant in most part is the costs money. You're going to involved (to have a) specialist to do a surgery and also the – essentially the inconvenience to go to a place to have the surgery.

So, with all those four criteria – so four parameters in it and essentially with this – it's determined with us and also the other people, leaders in the field is that we'll need something with actually with a very high sensitivity.

And also, because that – OVA1 actually is the first ever clear test by – clear test by FDA for multiple protein biomarker combined as a single index assay, so part of the thing for FDA is the efficacy and safety is really issue and have the highest sensitivity looking under this criteria and make the it easier to treat, through the whole process.

So it is by design that the – we choose a relatively high sensitivity somewhere around 90 percent to 95 percent (that really depends on the different) dataset, but highest sensitivity and then to – for that cutoff.

Once the cutoff is decided, we went through multiple studies, including the second – the company one, multiple studies and other people the sensitivity is more or less the same American system is high.

And I think part of the other things I want to say about it is that, because it's not meant to be as a diagnostic decision as essentially whether you have a disease or not, it's more as a differentiation about risk.

And I think the key thing to look at is the – all those population prior to the test the prevalence is somewhere around 20 to 30 percent. And after the – after the test, we actually the original validation study has a higher prevalence of 31 percent.

After the – when the test is positive, the PPV is 42 percent. So it's about a 10 – 11 percent improve – enrichment of the cases in the test positive population. However, because the design with a very high sensitivity, the actual predictive value is about 92 percent for the – 92.7, so it's about 93 percent.

So, essentially, before the test, you have a 30 percent or 31 percent chance of having cancer. After the test a chance to reduce to about 3 percent. So that's – it's about a sevenfold or so more reduction.

The second validation study by Bristol and their group, that is the prevalence before the test is about 18.6 percent. After that, if they are positive, the – it probably becomes 31 percent. But if you are negative, the probability is less than – less than 4 percent.

So again, it's a significant reduction and that's actually the key point that when it's designed for the purpose it's not by chance. It's actually before the study and the algorithm derivation we made a decision that's where we want to go and wait for that.

The other issue is the analytical precision of the test I want – I'd just quickly go through. But it is also a first because the first ever be cleared by FDA and I actually worked with the head statistician of FDA to come up with – she made a suggestion and I made some modifications and eventually did that.

Essentially, each showed individual analyzed goes into the OVA1 algorithm has a precision profile essentially what's the CD and across the entire range. Then, we have the actual clinical study population, the patient that you have the – like if you have the five and the last values.

And for each value, end of that value because we know it could be analytically very up and down by chance. So we use something called Monte Carlo simulation to generate data around those points similarly when the assay has variation for this particular patient how it's going to affect the OVA1 results.

So – and this is always all the patients across the whole study sections and it generates lots of point. And that's actually the – at the end, the – with the exception of one place around OVA1, you could do four.

The CV is about a 6.4 percent. The rest are across the range 5 percent. Actually, the CD is less than the individual analyzed CD. And the – because of that work, actually, I think it has become an acceptable method for all those (IDDMI) precision analysis for all our people in the field.

So finally, to summarize, the point I want to make OVA1 combines the markers with complementary barriers that include overall performance. So, in some way, actually it covers better than individual markers for us just because of the use of multiple markers.

And the other thing is that, actually, we were able to show – and actually, it's also a derivation process that make OVA1 has a very high assay precision. That's all I have for that.

Ola Awodele: Thank you very much, Dr. Zhang. I actually have a couple of questions. It could be one, it could be two, but I'll ask them. And while I'm asking that, operator, if you could – before I start asking, if you can just queue up and ask the CAC members if they have any questions so that we can start to have them come into queue. And, after you finish that, I'll then start my own –asking my question to Dr. Zhang. OK. So if we let the operator ask.

Operator: Once again, as a reminder, if you have a question, press star, then the number one on your telephone keypad. Again, that is star one to ask a question.

Ola Awodele: Thank you, Jamaria. OK. So, Dr. Zhang, thank you very much for the presentation. I do have a couple of questions. The first one is you did mention that there were small population sizes for most of these studies.

And my first question is, especially in light of what Dr. Cherot had said earlier, was there an ability to separate out these – in terms of analyzing the data taking into consideration the fact that different ethnic groups, especially African-Americans like she had mentioned have potentially CA125 results that could that vary – that reliability of CA125. Was that – was there an ability to look at your data from that aspect as well when you are evaluating OVA1?

Zhang: The original – when OVA1 gets to FDA clearance validation study and there are a prototype and also the ethnic group information, which I wasn't prepared for that question, so I didn't have the list in front of me.

But let me – let me tell you this. Essentially, my impression again because we – each individual study, the actual subtype because in the – in the U.S. is those – they don't issue one of the studies. They may not have a sufficient number to validate multiple study we saw this to be a very consistent pattern that I (see) OVA1 was able to detect.

Ola Awodele: OK. And the reason I asked is because, as you know, with OVA1 ROMA and Overa, the common – the common thing in all of three of them is CA125. So I'm just asking how we're able to come up with the decision that, you know, it's the test and not the CA125 that's also still end up having some effect in there, how are we able to account for that because I thought that that was really interesting that in OVA1, Overa and ROMA, as much variation that they had, CA125 was something that was common to all three of them.

Zhang: Let me answer that question. One is actually some of that I was not able to show one of the slides I had is that when I was talking about the 1,800 patient before we went into the development of OVA 1, 1,800 patients, those – the way that we are able to separate the patients made the decision, actually those markers do not have CA125

in it that prove those markers have a value for discriminating my intent from the other.

However, why you actually do the product development, there's no reason not to include in CA125. And, as a matter of fact, CA125 was most contributory among other biomarkers.

The other one is what happens for those is that the – when we – well, I'm going to technical details – when you combine multiple markers, it's not necessary to the markers to combine together.

It would always better than one good markers and have the not-so-good markers together because it just needed to be complementary. It's the two very good markers, but if they happen to be very overlap, they miss the same patients and the combination may not be as good as the one that was left.

The other markers that are involved, a lot of them actually are not necessarily as if we look at what they are and not necessary as that they're actually as a driving force of causing the ovarian cancer and more as the result of having ovarian cancer.

So that's some of the – yes. I don't know if I get into the technical part of that. But in a way we were able to see especially for the premenopausal part they are significantly better than CA125.

Ola Awodele: OK. Thank you very, very much. I really appreciate you making time today to attend the meeting and to give the presentation. So thank you very much. And I do not see any further questions.

Zhang: OK.

Male: Dr. Awodele?

Ola Awodele: Yes?

Male: This is Dr. Haug. I just had a couple – a question. Earlier, a mention was made of the UpToDate. And in the section on the evaluation of an adnexal mass, there is a chart that refers – is referral of women with pelvic mass to a GYN oncologist ACOG guideline.

Now, these guidelines do say 2011, but these are the ones that are listed in the current UpToDate which is (enlisted) as last updated in March of this year. And it has two different sections, one for premenopausal women and one for post-menopausal women. But the only marker that's listed is an elevated CA125. It doesn't mention anything else.

And the other thing nobody has mentioned NCCN guidelines. And I – in the workup of a suspicious – you know, a suspicion for ovarian cancer in the section and workup OVA-1, it has CA125 or other tumor markers as clinically indicated and then has a footnote, but the footnote doesn't include – doesn't look like it includes OVA1 or ROMA.

It also – I don't know if anybody could comment on that – on those two things, my observation about what's listed currently in the UpToDate and the lack of mention of OVA1 in the NCCN guidelines. That's all I had.

Ola Awodele: Thank you, Dr. Haug. I don't know if any of them are still on the line, but I will mention that I also – what I – what I noticed with that is the fact that what is clearly indicated in terms of NCCN and ACOG guidelines is the fact that a GYN onc should be doing the surgery if malignancy is highly suspected – if suspected, so for better outcomes.

But, like you, OVA1 is not mentioned in the guidelines. And not only that, actually online – accessible online is the fact that OVA1 had actually requested to be included in the guidelines and that had been voted down by the NCCN Ovarian Cancer panel about two or three times. So I just wanted to mention that in answer to your observation there.

OK. So thank you. Operator, I'm going to move – OK. So we – I do have a question from a Dr. Eric Loo. Could you please open his line please?

Operator: And hi. And Eric Loo's line is open.

Eric Loo: Hello. I'm a pathologist over that Dartmouth. I – this is not my area of expertise, but I think you might have been looking at the wrong UpToDate because I have that open right now too.

And OVA1 and ROMA and those items Overa are also listed under the UpToDate write-up called Serum Biomarkers for Evaluation of an Adnexal Mass for Epithelial Carcinoma of the Ovary, Fallopian Tube or Peritoneum. So you might have been looking at the wrong one. And the NCCN guidelines look like they also mentioned it. But I hadn't had the chance to really look at that very clearly. That's all I wanted to say. Thanks.

Ola Awodele: OK. The latest NCCN guidelines are 2.2019 and actually they don't – even though the section say it's OVA1, not to be – not to be confused with OVA1 – they actually do not list OVA1 as one of the recommendations.

Eric Loo: OK.

Ola Awodele: But we certainly, you know, revisit that. Thank you for pointing that out. OK. There are no other questions in the OK. So I'm going to move on to the next section. So if you can mute – operator, if you can close the lines of Dr. Zhang, Dr. Cherot and Dr. Schulman, that would be nice – Schulman – that will be appreciated.

So I'm going to move on to the next section here and just talk a little bit about what we're going to do in terms of what to expect in terms of the voting aspect and everything and then we'll go on to the discussion.

So we're going to move on to the next one which – next section which will be to discuss the voting questions. And I just wanted to say that we won't be voting real time, but I would really appreciate that people would return the Excel spreadsheet that was sent out with votes using the Excel spreadsheet and return that within a week of today's meeting so that we can tally up the votes.

And I also want to say that individual voting is not – individual voting is not going to be released, but it's going to be an aggregate voting for (this record) – score that will be put – published online when the – along the minutes at a later date. So I don't know if Dr. Brewer was able to join. She was going to join since one of our CAC members – Dr. Brewer – I don't see her name. OK.

Female: Yes. I'm on the line.

Ola Awodele: You are? Thank you very much, Dr. Brewer.

Female: Yes. I've been on – I got – called in just a couple of minutes late, so.

Ola Awodele: OK. Yes. You had – I really appreciate you coming on. So do you have any comments or anything that you would like to say concerning what – I don't know, what all you were able to hear so far?

Female: No. I heard – I heard – no, I heard everything. And I guess, you know, from my perspective, I went through this whole bibliography fairly carefully. And the data is really all over the place.

And I think the two most important papers from my perspective are Laura Havrilesky's paper, which looks at the cost effectiveness for women with an adnexal mass. And her conclusion was that referral of all patients with a complex ovarian mass is the least expensive and that all of these patients ended up getting managed by a gynecologic oncologist.

And Dr. – and Kim – I don't know his first name. It was a 2012 paper, showed essentially the same thing. And so, I follow this OVA1 literature pretty carefully. And their sensitivity is high, but their positive predictive value, they essentially don't report most of the time.

And that's the thing that I'm the most interested in. So I think that – you know, I think that OVA1 misses some patients. I think it overcalls some patients. I think that's true of all of the – all of the things that we have in our armamentarium, but if we're looking at cost effectiveness and best practice, I just – I can't endorse the OVA1 as being the number one test.

Ola Awodele: OK. Thank you – thank you very much. Is there anybody else that wants to debunk what Dr. Brewer said or add to it or comment on what she said? Operator, could you ask?

Male: This is Dr. Clark. I just like to ask Dr. Brewer if she could be a little more specific on what she said. I think the first statement you made was one that – I don't know whether you heard my statement earlier.

But basically, I was just talking about the wisdom of referring all post-menopausal complex ovarian masses or treating all of them as though they are cancer until proven otherwise, which means managing them as an oncologic surgery. I think we're in agreement. Is that what you just said?

Female: That is what I just said. And, you know – and I speak – and I'm an oncologist, and so, I speak from that perspective that I would rather – I would rather evaluate these patients than have them be missed.

And so, if you use – post-menopausal women are at the highest risk for having a cancer. And I think that – I think it's – I think it's appropriate to refer them. That's part of what's been shown through SGO and ACOG is that these patients should have a low threshold to referring these patients.

Male: Thank you. So I appreciate that. Thank you.

Ola Awodele: Thank you. Anybody else on the line? Operator, can you check if anybody else on the line has any comments or questions?

Operator: Absolutely. If anybody would like to ask a question or pose a comment at this time, press star one on your telephone keypad.

Ola Awodele: OK. Dr. – could you open up Dr. Bob Babkowski's line please?

Operator: Absolutely. His line is open.

Robert Babkowski: Yes. Hi. This is Dr. Babkowski again. I have a question – just a general question. You know, I do believe the data does support the observation that these tests are better than just using CA125 as a test.

So I think from a – from a pathologist perspective, I think the analytical positive predictive value, OK, is higher with OVA1 than CA125. So when I look at it in terms of a better – of – you know, the next – and I'm thinking of it as a more of a next-generation test.

The – my biggest concern, quite frankly, about this whole assay is that it's going to wind up being overused by docs who, quite frankly, I'm going to say using it as a screening test. And I do think it needs to – it needs to be used to, quite frankly, like in my institution, what I'm – what I've noticed is that having the GYN oncologist on standby on the cases that are – that are more likely to be positive where this assay becomes useful.

And again, it's a transfer of the patient to the right location, so it's more of a patient triage tool than anything else and I think there's value in that. You know, then observations about using the test for that purpose I think are pretty valid although I do – I see your point about the data being somewhat scattered.

And I think that's part of the reason, by the way, why it didn't make it into the NCCN guidelines. So what are your thoughts on it? I mean, is this the – is this the better (mass trap) essentially? Is this a better alternative than CA125 because that's the question? Because, for me, it really is.

Female: Well, I think it depends on what parameters you're looking at. And I think – I think the sensitivity of OVA1 is a little bit higher. I think the false positives is also higher in OVA1. I think that, you know, CA125 in the post-menopausal population is pretty good.

And if you look at the characteristics of – and this is something I didn't mention – but if you look at the characteristics of the mass on ultrasound, that's also pretty good in terms of who needs to be referred.

And so, you have to look at the whole patient. You have to look at all of the parameters. And I agree with you. I think that what I see as a lot of people are using OVA1 as a screening test and it's not appropriate, you know, 15 years ago they tried to get it approved and we at SGO came out pretty strongly and basically said there's not any data to use this as a screening test.

So I think that you have to – you have to look at the whole patient. Every test you do is going to have false positives and false negatives. And if you just rely on one test to make a decision, I don't think that's good medicine.

Robert Babkowski: No. I agree on that. Yes.

Ola Awodele: And I'm – thank you very much. And I also wanted to chime in. I wanted to ask you, Dr. Babkowski, you had mentioned and maybe I misheard you. You had said something about the positive predictive value or did you mean negative predictive value was high because you had said that it was the positive.

I tend to agree with Dr. Brewer more from the literature and from what I read that it's – it has a – it has – it's more of the high negative predictive value that could useful as opposed to a positive predictive value.

Robert Babkowski: No. That's – yes. I – that's what I meant. Sorry.

Ola Awodele: OK. I just wanted to make sure.

Female: Yes. And I would – I would agree with you on that.

Robert Babkowski: Yes.

Ola Awodele: OK. All right. So let me then ask you one of the questions that we have on here is how confident are you that there's adequate published evidence that the conclusion of – the conclusion of the test below are generalizable to the typically Medicare patient population of 65 and older which kind of piggyback some of what Dr. Clark had been saying when essentially we're talking post-menopausal.

So how confident are you on that, that there is – what do you think about that in terms of published evidence that we have for our own typical population of Medicare which is 65 and older?

Robert Babkowski: Well see, that's where I think the data is kind of lacking which is why I asked the question because I do think – I think this test is probably more useful in the under 65 than over 65. I don't think I have enough data to make that decision.

Female: Yes. I would agree 100 percent.

Ola Awodele: OK. All right. And, operator, could you just see if there's anybody else who has a comment or would want to – I mean, from our CAC members who would want to join in this discussion so we can open up their line as we speak, please?

Operator: Absolutely. If there is anyone else that has a question or like to pose a comment at this time, they can press star one.

Ola Awodele: OK. And while we're waiting on that, for Dr. Babkowski and Dr. Brewer, how confident are you about the – that there is adequate evidence that have been published that would aid in the assessment of likelihood of malignancy in women presenting with an ovarian adnexal mass prior to plan progressing?

I think what I'm trying to see is what I head Dr. Brewer say and I tend to agree is there is – you have to take in the clinical presentation, the clinical picture of the – of the woman – and also, the ultrasound and the nature of the mass and all of that.

And then, if you're still – I mean, according to the test, if you are still doubting that it's malignant, because I think what we have tried to established here is that, if you think it's malignant after all of that, you really should be referring to a GYN onc.

But what these tests are saying is that if you are then still doubting or you feel like it's – you're leaning more towards negative, then you should do the test. And from what I'm reading, if it still is negative, then go ahead and do the surgery yourself. But if it's positive, go ahead and send them to the GYN/onc. Would you say that's pretty much what that is or what is your take on that?

Female: I think that's a reasonable – I think that's a reasonable assessment.

Robert Babkowski: Yes. I concur.

Ola Awodele: OK. Thank you. OK. Could you open Dr. – I mean, could you open Dr. Loo's line, please, operator?

Operator: His line is open.

Eric Loo: Hello.

Ola Awodele: Thank you, Dr. Loo.

Eric Loo: Thank you. I just wanted to get clarification because it sounded like – and what you guys had just said as well that the screening test was really the clinical exam plus the ultrasound finding the adnexal mass and that this test was supposed to be used to determine whether or not the patient needed to be referred to a specialist for their surgery.

I'm not too clear as whether or not the cost of doing this test would outweigh the additional burdens being placed on the specialists or not. Would anybody be able to clarify that?

Ola Awodele: So the FDA label – I just wanted to quickly jump in here and then I'll Dr. Brewer and Dr. Babkowski answer if they so choose – the FDA label specifically says that the person has to be 18 or older. You already have the mass and you've already made a decision to go to surgery. So all three of those things exist. And then, this test may be done to make sure – so the indication is to make sure that a GYN/onc does the surgery if it's – if it's malignant for better outcomes.

Eric Loo: Sure.

Ola Awodele: Dr. Loo?

Eric Loo: The question is it – is it just cheaper to do the test in that situation rather than, you know, send the patient to a GYN/onc specialist? I think…

Ola Awodele: So are you saying that is it cheaper – like if you do all of that and you – you're highly suspicious of or you're not suspicious of malignancy…

Eric Loo: Right.

Ola Awodele: Rather than…

Eric Loo: A better use of resources to do this test and spare the patient being referred to a specialist in the, you know, clearly-defined situation that was on the (gate), like what…

Ola Awodele: Well, we're – this meeting is really to discuss in terms of the literature concerning – it's evidentiary. We're trying to look at the evidence and the literature that's out there and discuss that.

Eric Loo: Sure. OK.

Ola Awodele: So that's what I would say to that. But, Dr. Brewer, Dr. Babkowski, do you have anything to add to that?

Female: Well…

Robert Babkowski: Again, I think there is merit to the test, but it's got to be very clearly defined. And well, the practicing OBGYN person – let me – let me ask you a question. Is there an issue with access?

Do you think there's an issue of access or adequate triage with the post-65 population? And again, I'm focusing post-65 because really that's the NGS-covered lives – population. I mean, is that – you know, because again, honestly, in my neck of the woods, getting access to a GYN oncologist is not difficult, getting GYN coverage is not difficult.

Female: (Inaudible) where I am either.

Robert Babkowski: Right. So…

Female: And another thing is, is that if you get into the rural – I mean, some of the data shown, if you get into the rural areas, the referrals are not – I mean, a lot of women are not managed by GYN/oncs, but they're – doing this test wouldn't increase their referral to GYN/oncs is the problem.

Robert Babkowski: Right.

Ola Awodele: So I think if we go back to the premise that's 65 and older, so post-menopausal with a mass, right, increases the likelihood of the – of it being malignant, what would – what – would doing this test really decrease the number of people going to the GYN/oncs?

Female: I'm not convinced it would. I mean, and then – and – but you're also talking about – it's not just a pelvic mass. It's a complex pelvic mass with high-risk features, right.

Ola Awodele: Yes.

Female: I mean, a simple cyst, you don't need to do this test on.

Ola Awodele: OK. All right. So I think we've discussed this, but I'll just – I'll ask again. In terms of the analytical validity, in terms of the literature that is out there right now, how confident are you in the methods that were used?

Female: I don't think most of the studies have large-enough numbers.

Ola Awodele: OK. So, in my – in my review of the literature, I would have to agree with you that that was the population. The other thing that I want to bring out is that a lot of the studies in terms of OVA1, there were – they used the same – there was overlap of the subjects, right. So there were – there were three or four papers that came out of the same, right – the same…

Female: The same cohort.

Ola Awodele: Right. The same – the same – yes. The same set of people. So it really made that a little bit difficult, if you would. So the studies – the studies contain small sample sizes like you had said.

They were overlapping patient populations. They were studies that were funded by the test manufacturer and they were – the studies included patients that actually were evaluated by a GYN/onc which I think kind of skewed this then.

Female: Absolutely, I think so.

Ola Awodele: It skew – it skews it because they were actually evaluated by a GYN/onc, so – and it's the whole reason to decide who goes to a GYN/onc if the GYN/onc is already evaluating the patient. And I think that's a skewed result. So as far as clinical validity there, those are the questions I would have. Dr. Babkowski, did you want to comment on that?

Robert Babkowski: No. I mean, I'm agreeing with the comments that are being made. You know, I wish the data was a little bit robust.

Ola Awodele: OK. Well, any other comments from the three of you?

Female: I don't think. I think it's been a good discussion.

Ola Awodele: Thank you very much. Operator, could you ask one more time if there is anybody on the line that would like to make a comment?

Operator: Absolutely. If anyone else would like to make a comment at this time, please press star one.

Ola Awodele: OK. It doesn't like there's anybody. This has been a short meeting and, once again, I would like to thank everybody who was able to call in and has participated. I really appreciate you taking the time to do so.

So I just wanted to remind everybody that my voting members, in terms of CAC members, to please submit your results within the week, the sooner the better. Use – submit the results using the spreadsheet that was emailed to you.

If you need us to resend one for you, let us know. We would gladly do so. And I also want to remind you that only the aggregate, not the individual scores that we publish. And I proudly urge you, like I said before, to use the Excel spreadsheet.

So I'm sure I speak for, you know, my colleagues and for NGS. Then, we really appreciate people taking the time and everyone's participation in today's CAC. It will surely provide invaluable perspective and information that will inform our future policy.

So I had mentioned earlier on that, at the end, if I had time, I would – I would say something about the process. So the next thing now would be for us to just go maul over all this information that we've received and the evidence and stuff and at a future date come up with a draft policy which will then be posted publicly to be presented at a future open meeting.

And so, I strongly recommend that people stay – keep posted by visiting our web page often to see if there's any activity and what that is there. So that brings us to the end of this CAC meeting and I guess I can say I gave everybody back 45 minutes of their life. And I, once again, want to say thank you very much to all of you especially Dr. Babkowski, Dr. Brewer and Dr. Loo. Thank you very much.

Operator, you could – you could now disconnect the call.

Operator: This concludes today's conference call. You may now disconnect.

Ola Awodele: Thank you, operator.

Operator: You're welcome.

END