Anthem, Inc.
Moderator: O'Bannon, Laketa
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Operator: This is Conference # 5788429.

Operator: Ladies and gentlemen, thank you for standing by and welcome to the Appended Open Meeting for Vermillion. At this time, all participants are in a listen-only mode. After the speaker's presentation, there will be a question-and-answer session. To ask a question during the session, you will need to press star one on your telephone. Please be advised that today's conference is being recorded. If you require any further assistance, please press star zero.

I would now like to hand the conference over to your speaker today, Dr. Cunningham. Thank you. You may begin.

Carolyn Cunningham: Thank you, operator and welcome, everyone. We were glad that we can have this Appended Call, so that we can hear Dr. Shulman's presentation and get it recorded and make it available with the recording of the other meeting. Dr. Shulman, you are welcome.

Dr. Lee Shulman: Thank you very much, Dr. Cunningham and everybody else, good morning. I thought what I would do is first read my statement and then at that point, at the end of my statement, I had somewhat of an algorithmic process that I've put that together into the slide presentation and we should still have plenty of time for questions. So if that's okay with you Dr. Cunningham, I'll get started.

Carolyn Cunningham: Please go ahead.

Dr. Lee Shulman: All right. My name is Lee Shulman and I'm the former Director of the Northwestern Ovarian Cancer Early Detection and Prevention Program. Having stepped down in September 2008 from my administrative responsibilities, after heading the program for 12 years. NOCEDPP – I know that's a mouthful but that's the abbreviation – is the largest such program of its kind in the United States. Since 2006 when I assumed the directorship, we have provided counseling and care to over 3,500 women who are at increased risk for developing ovarian cancer either as a result of family history or as a result of inheriting pathogenic variants in cancer predisposing genes.

It's become clear for some time that even in this high risk population, CA-125 alone provides an inferior approach to screening such women in situations when they present with an adnexal mass. The lack of clinical value of CA-125 in the community based risk, encompassing actually most women in the United States is well known and is considered to not only be a [poor] test to aid in the assessing a risk for ovarian cancer prior to surgery but actually is considered to be harmful.

This is true regardless of whether they are pre or postmenopausal. Indeed, the problems with CA-125 in all women are two-fold. First, many women who are eventually found to have cancer have little to no increase in CA-125 levels. And second, and perhaps most concerning, is the frequency of elevated CA-125 levels in women without malignancy.

Organizations such as ACOG and the Society of Gynecologic Oncologist, those organizations that provide guidance for the care of women either predisposed to cancer or women in general who have unanimously rejected the use of CA-125 alone in the evaluation of these women and have strongly supported the use of MIAs or Multivariate Index Assays for the evaluation of women who present with an adnexal mass.

Preventing the use of such MIAs for postmenopausal women with adnexal masses would not only provide substandard care to these women but would increase unnecessary surgeries for these women and likely increase the frequency of advanced ovarian malignancies by missing early ovarian cancers. As such, this decision would profoundly increase the morbidity and mortality for actually no good reason given the proven effectiveness of FDA-cleared MIAs that have a superior clinical outcome for women presenting with adnexal masses regardless of menopausal status.

I hope that the robust study supporting the use of MIAs in all women including post-menopausal women will guide the decision to support its use for all women presenting with an adnexal mass regardless of the age or menopausal status of that woman.

So that concludes the formal statement. If it is okay with you, Dr. Cunningham, I'd like to start in as soon as I can pick it up with my slides.

Carolyn Cunningham: Please go ahead.

Dr. Lee Shulman: They went away. Let me see if I can – two seconds – and here we are. Good. So assuming everybody can hear me, you can go to the next slide, please. So my financial disclosure is pertinent to this presentation as I am a consultant to Vermillion ASPiRA Labs.

Next slide, please. So how is ovarian cancer diagnosed? Well unfortunately, it is typically diagnosed in an advanced stage after certain nonspecific signs or symptoms are related. Typically, bloating, abdominal pain, a change in weight – sometimes a loss of weight, sometimes an increase in weight but in verily those

signs and symptoms occur well after the early stages of ovarian cancer have passed. And so frequently, it is left to the primary care provider to assess those symptoms. Again for those who may not be skilled in these particular issues in women's health, a profound delay can frequently occur and unfortunately does often even in tertiary care centers like here at Northwestern.

Eventually, a transvaginal ultrasound or perhaps an MRI or CT will diagnose in adnexal mass. A transvaginal ultrasound is an ACOG level-A recommendation for the evaluation and management of adnexal masses. That is when that mass in the adnexa encompassing the ovary, the tubes, or the paramesonephric area between the tube and the uterus is found to be enlarged on pelvic exam or perhaps as a primary approach when symptoms have occurred and some sort of imaging is obtained to evaluate those symptoms.

Interestingly enough, a minority of those adnexal masses are either clearly benign or clearly malignant. Obviously, benign cases do not need surgery for the most part, unless they are very large adnexal masses in which torsion is a concern. A watchful waiting can be done. A repeat ultrasound and depending on how big this adnexal mass is or what it appears to be in several weeks to several months. Clearly malignant cases, however, should be immediately referred to a gynecologic-oncologist and for surgery and further evaluation and treatment.

Now, in saying that a minority of cases are clearly benign or malignant, that means the majority cases will be let us call them indeterminate. Some of these indeterminate cases will require surgery depending on imaging and symptoms, some of these cases will be malignant but perhaps what is most important is that as opposed to other cancers, a biopsy procedure to ascertain the malignant potential of that mass is a profound contraindication primarily because a needle biopsy, that can be potentially performed under ultrasound guidance. In the case of malignant tumor, would spread malignant cells into the abdominal cavity and result in an upstaging of that particular presentation.

Most ovarian cancers as such are diagnosed during the surgery for the adnexal mass – so if I can go or maybe I can switch it up, thank you – I'm not going to go through this clinical algorithm but let us say, we find this adnexal or pelvic mass detected on ultrasound and perhaps initially detected through a pelvic examination ultrasound has confirmed an adnexal mass, if it is clearly benign on the left, usually under 10 cm because a 10 cm, we get concerned about gynecologic conditions like torsion, not malignancy conditions but if it appears simple, no blood flow to it, the risk of malignancy is very small and we would likely monitor this patient to see whether this further grows or doesn't.

On the extreme right, the clearly malignant – again, a large cyst with complexities within the cyst wall, blood flows directly to the cyst area, clearly this patient needs to be referred to a GYN-Oncologist. And then we go into the majority here which is everything else. It doesn't necessarily appear malignant, doesn't necessarily appear benign, and at this point, the ACOG, which provides clinical guidance to women's health care providers, recommends a level-B assessment and in this situation, they recommend not CA-125 for reasons that I mentioned earlier. And in addition to the fact that it is not a test that is FDA-

cleared for that particular use. The only approved FDA clearance for CA-125 is to monitor the progression of ovarian cancer after it has been diagnosed, not before it has been diagnosed.

And so what ACOG and other organizations recommend promote through the literature that has clarified the improved use of these MIAs or again Multivariate Index Assays that would then give the OB-GYN valuable information as to whether or not there is elevated risk for malignancy in which case, we refer that patient to a GYN-Oncologist or a cancer surgeon depending on the availability of that and which area this patient may reside or a low risk of malignancy in which case, the OB-GYN will treat, perhaps take to the operating room for further evaluation.

Next slide, please. So what is the challenge here? Well, first, perhaps people would say, "Well, why don't we just refer everybody to a GYN-Oncologist? Well, can't do that. There are approximately 300,000 women who present with an adnexal mass in the United States each year. There are only several thousand GYN-Oncologists. It would make for an impossible situation. It would not permit that GYN-Oncologists to take care of those women who truly need their service, meaning those women who have cancer or a very high risk of cancer.

At the same time, appropriate referral is critical because once we have detected this and perhaps detected it without symptoms, we have potentially the ability to diagnose this ovarian cancer at an earlier stage, at a stage in which survival is markedly improved. Now, as you see here in the first bullet, early stage diagnosis is key. Well over 65% close to 70% of ovarian cancers are diagnosed as stage III or stage IV. 5-year survival is not only less than 30% for stage IV, it's less than 10%. And for stage III cancer is probably in the range of about 20% to 25% by some estimates.

Okay. If that is the case, let's everybody do the surgery and then for those patients who have cancer, we can get them to the GYN-oncologist. Well, that doesn't work either because we now know and again work that had been done at large centers throughout the United States show that when that patient is referred before the initial surgery is done, so while there is the adnexal mass, while there is the concerning ultrasound findings; however, that woman is evaluated to be at increased risk or again more common – more frequently now with MIA analysis. When that woman gets to a cancer center and is operated on by a gynecologic-oncologist, her outcomes and survival are markedly improved.

So I mentioned a little bit earlier how it's important not to do a biopsy and close things up. Unfortunately, that still occurs in the United States and even here in Illinois and it is estimated that that process a biopsy in an open procedure or laparoscopic procedure and then closing the patient up perhaps reduces her 5-year survival regardless of the stage by anywhere from 25% to 30%. So again, we don't want that OB-GYN to be surprised when in fact he or she is found an adnexal mass did not do a thorough evaluation. Perhaps the CA-125 that was "normal" to find that there is a frank malignancy when they enter the abdomen,

and there is no skilled oncological surgeon, GYN-Oncologist, or cancer surgeon to be able to do the appropriate staging for that particular patient.

Next slide, please. So ACOG – again the organization that provides clinical guidance to OB-GYNs around the United States and around the world – have level-B recommendations. Now they have still included CA-125 in that recommendation except for the fact that both – the other two options OVA1 and ROMA are in fact both cleared by the FDA for the evaluation of this and CA-125 is not. I mentioned this earlier, it is only an FDA cleared test for evaluating ovarian cancer risk, risk of recurrence in women who've already been treated for ovarian cancer.

The reason why it is still used to the extent is that it has essentially been until the last several years. The only despite the fact it is shown to be substandard, the only laboratory evaluation that could provide some sort of meaningful information but again literature comparing OVA1/ROMA with CA-125 consistently demonstrates that OVA1 and ROMA are far superior to CA-125 both with positive predictive value and perhaps is importantly with negative predictive value. And in this situation, negative predictive value was critical because we want to be able to say that that adnexal mass in that woman is likely not malignant, so that when she is operated on by her generalist OB-GYN skilled surgeon but not a skilled cancer surgeon, that physician is likely not going to be surprised with an overt malignancy when she or he enters the abdomen. So again, for both sensitivity and perhaps more importantly specificity, OVA1, ROMA, those MIA analyses as well as complex algorithms provide a far superior triage assessment of that woman with an adnexal mass.

Next slide. So the problem – that reason why we are on the phone today is that at this point, NGS is prohibiting all ACOG level-B recommendations and as such, ROMA is not covered by NGS. OVA1 is currently not covered by NG. And at this point, clinicians are left without an appropriate assay to evaluate that person with an adnexal mass. What that means is two-fold, very simply.

Many women, again the majority are going to have an adnexal mass as indeterminate, are either going to be waiting and allowing an early malignancy to progress or unnecessarily referring a patient to have surgery that she ultimately did not need and as a result, clogging up the GYN-Oncology [system], exposing the patient to needless morbidity and even mortality. In a sense if we go to the bottom bullet, it is maintaining and reaffirming the status quo which we all know is not adequate and is not appropriate.

Next slide. So status quo in a sense reduces the likelihood of early stage diagnosis and improved outcome. Status quo either refers inappropriate patients to the GYN-Oncologist or refers patients only after the malignancy has been allowed to advance and again without the coverage for OVA1 and other MIAs as well as ROMA, the status quo is maintained and women will continue to in my opinion and most other people's opinion suffer needlessly. The increased morbidity and mortality that ovarian cancer does present even in cases that are

optimally evaluated and cared for only making that particular morbidity and mortality rates unnecessarily more adverse.

And my final slide, please. So again, OVA1 in particular is FDA cleared for and is particularly used for providing a triage assessment of a woman with an adnexal mass. It does so for women of all ages. It does so for women of all menopausal status. It has the highest ovarian cancer sensitivity for early stage disease in all aged women of all cancer types and in a recent study, clearly provide superior triage assessment in African-American women who for a variety of reasons I think is well known have had some of the worst outcomes of ovarian cancer for access to healthcare and a variety of other things.

For me as somebody who sees in the range of about 40 to 50 women at risk for ovarian cancer each week in my office, it has the highest negative predictive value which is such an important thing, determining not so much when to send the patient to the GYN-Oncologist which it is but reaffirming when that patient's findings are likely not associated with malignancy, so we don't have to make the needless referral and expose the patient to needless surgery. And it's available right now.

This is not something that is in the work that is being evaluated, has already been cleared by the FDA for this particular use and clearly what I have seen in my own practice and the practice here at Northwestern and in Chicago in general, it clearly is helping to change the status quo, improving outcome for women.

So with that, I will stop here. I made it under 30 minutes. I'm very proud of myself. I'm happy to answer any questions.

Operator: As a reminder, to ask a question, you may need to press star one on your telephone. To withdraw your question, press the pound key. Please stand by while we compile the Q&A roster. Your first question comes from the line of Charles Dunton.

Dr. Charles Dunton: Hi. My name is Charles Dunton. I'm a GYN-Oncologist. I was there at the Chicago meeting and had a chance to present but not as much as I would have. I would have liked to have had some more time, so I just want to make a couple of comments. I agree with Dr. Shulman. I am employed by Vermillion, that's my financial disclosure but some of the data I wasn't able to present the [inaudible] paper, which we'll get you a copy of, clearly shows that there were 86 early stage cancers in his study. CA-125 detected 54 and OVA1 detected 79, so you can see the difference there.

Additionally, the ACOG practice – I'll just read from that the Multivariate Index Assay has demonstrated a higher sensitivity and negative predictive value for ovarian malignancy when compared with clinical impression in CA-125 and gives the data on 494 women going 91% sensitivity for OVA1 and only 65% for CA-125. And they end up with a false negative rate as less than 2% when the results of imaging and the Multivariate Index Assay indicate low risk.

So that's right in the ACOG clinical guidelines. And also Dr. Shalowitz talking about access to care, they went through databases and looked at 36% of counties are further than 50 miles from the nearest Gynecologic-Oncologist and a total of 14.8 million women live in low access counties and approximately over 7,600 women with gynecologic cancers experience geography-related disparities and access, and 40% of hospital referral regions do not contain the primary [inaudible] of the GYN-Oncologist.

So it is important to have a test like OVA1 that can get the patients to the right doctors, pick it up with higher sensitivity, and allow the gynecologist to feel comfortable with a negative predictive value. So I just wanted to make those comments and I thank Dr. Cunningham and NGS for allowing me to do that. Thank you.

Carolyn Cunningham: Are there any other questions or comments?

Operator: And again, if you would like to ask a question, press star one on your telephone. To withdraw your question, press the pound key. Please stand by while we compile the Q&A roster. And there's no further questions in the queue at this time.

Carolyn Cunningham: Thank you, Operator. Thank you, Dr. Shulman, and our other speakers. I think this will conclude our call.

Dr. Lee Shulman: Well I appreciate the opportunity. Have a great day, everyone.

Carolyn Cunningham: Hope you do too.

Dr. Lee Shulman: Thank you.

Operator: Ladies and gentlemen, this concludes today's conference call. Thank you for participating. You may now disconnect.