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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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MICROBIOLOGY DEVICES PANEL

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March 12, 2014
8:00 a.m.

Holiday Inn College Park
10000 Baltimore Avenue
College Park, MD 20740

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ANGELA M. CALIENDO, M.D., Ph.D.	Panel Chair
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ROBERT BURK, M.D.	Voting Member
KIMBERLY E. HANSON, M.D., M.H.S.	Voting Member
LIZZIE J. HARRELL, Ph.D.	Voting Member
PAULA HILLARD, M.D.	Voting Member
KENNETH H. RAND, M.D.	Voting Member
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JOANNA M. CAIN, M.D.	Temporary Voting Member
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ELIZABETH UNGER, M.D., Ph.D.	Temporary Voting Member
ALAN G. WAXMAN, M.D., M.P.H., FACOG	Temporary Voting Member
CHERISE P. SCOTT, Ph.D.	Consumer Representative
GLEN P. FREIBERG, RAC	Industry Representative
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M E E T I N G

(8:00 a.m.)

DR. CALIENDO: Good morning, everybody. I would like to call this meeting of the Microbiology Devices Panel of the Medical Devices Advisory Committee to order.

I'm Dr. Angela Caliendo. I'm the Chair of this Panel. I am currently the Vice Chair of Medicine at Brown, and my expertise is in clinical virology and infectious diseases.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel members participating in today's meeting have received training in FDA device law and regulations.

For today's agenda, the Panel will discuss, make recommendations, and vote on information regarding the premarket approval application sponsored by Roche Molecular Systems, Incorporated, for the cobas HPV Test, which is a qualitative in vitro test for the detection of human papillomavirus in patient specimens.

Before we begin, I would like to ask the distinguished Panel members and FDA staff seated at the table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation.

MR. FREIBERG: I'm Glen Freiberg. I'm the Industry Rep on the Panel, and I've been in FDA regulatory affairs since 1976.

DR. SCOTT: Hello, my name is Cherise Scott. I'm the Consumer Rep. My expertise is in immunology and infectious diseases, and I work for the TB Alliance.

DR. PORTIS: I'm Natalie Compagni Portis, and I'm the Patient Representative on today's Panel.

DR. BLUMENSTEIN: I'm Brent Blumenstein. I am a biostatistician from Washington, D.C., and an independent consultant.

DR. HARRELL: I'm Lizzie Harrell, Research Professor Emeritus of Molecular Genetics and Microbiology at Duke University Health Systems. I was formerly the Associate Director of Clinical Microbiology at Duke, and I taught in the medical school. And my area of expertise is clinical microbiology.

DR. HILLARD: I'm Paula Hillard, Professor of Obstetrics and Gynecology, Stanford University School of Medicine, and my expertise is in the area of pediatric and adolescent gynecology.

DR. NOLLER: Ken Noller, obstetrician/gynecologist, Director of Examinations, American Board of OB/GYN, Dallas, Texas.

DR. HANSON: Hi, I'm Kim Hanson. I am an Associate Professor of Medicine and Pathology at the University of Utah. My clinical expertise is in adult infectious diseases, and I'm also a medical microbiologist and Director of the Clinical Microbiology section at ARUP Labs. My expertise is in molecular diagnostic testing.

DR. RAND: Hi, my name is Dr. Ken Rand. I'm Professor of Pathology and Medicine at the University of Florida. My expertise is in clinical microbiology, clinical virology, molecular test development, and clinical infectious diseases.

LCDR ANDERSON: My name is Lieutenant Commander Anderson. I am the Acting DFO for this Panel. I'm here to represent the FDA and the United States Public Health Service.

Thank you.

DR. BURK: Good morning. I'm Robbie Burk. I'm Vice Chair of the Department of Pediatrics at the Albert Einstein College of Medicine in the Bronx. I am in the departments of epidemiology and public health and obstetrics/gynecology and microbiology and immunology. My expertise is in human papillomavirus, molecular epidemiology, and genomics.

DR. CAIN: Good morning. I'm Joanna Cain. I'm Professor and Vice Chair of Obstetrics and Gynecology at the University of Massachusetts. My expertise is in gynecologic oncology.

DR. WAXMAN: I'm Alan Waxman. I am a Professor of Obstetrics and Gynecology at the University of New Mexico. I'm the immediate past president of the American Society for Colposcopy and Cervical Pathology. My expertise and area of interest is in cervical cancer prevention.

DR. BIRDSONG: I'm George Birdsong from Emory University

and Grady Hospital in Atlanta, Georgia. I'm Professor of Pathology at Emory, and my expertise is cytopathology and informatics. And I have been a president, in the past, of the American Society of Cytopathology.

DR. MASSAD: I'm Stewart Massad. I am Professor of Gynecologic Oncology at Washington University in St. Louis. My expertise is in cervical cancer prevention, especially guidelines for management of abnormal screening tests.

DR. SARAIYA: Good morning. I'm Captain Mona Saraiya from the CDC Division of Cancer Prevention and Control. I am a prevention medicine/public health physician, and my expertise is in cervical cancer screening and prevention.

DR. UNGER: Good morning. My name is Elizabeth Unger. I'm at the Centers for Disease Control and Prevention, in the Chronic Viral Diseases Branch, where the human papillomavirus laboratory is. My expertise is in the area of molecular epidemiology of HPV, and I am a surgical pathologist by background.

DR. HOJVAT: Good morning. My name is Sally Hojvat. I'm the Director of the Division of Microbiology Devices in the Office of In Vitro Diagnostic Devices and Radiological Health here at FDA, and my expertise is running a group that reviews submissions that are microbiology based.

DR. CALIENDO: Thank you.

I note for the record that Dr. D'Agostino will attend via

telephone conference, and Dr. Brent Blumenstein is attending as a Voting Member.

Members of the audience, if you have not already done so, please sign the attendance sheets that are on the tables by the doors.

And LCDR Anderson, the Acting Designated Federal Officer for the Microbiology Devices Panel, will make some introductory remarks.

LCDR ANDERSON: The Food and Drug Administration is convening today's meeting of the Microbiology Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the industry representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with the Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have potential financial conflicts when it is determined that the Agency's need for

a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss, make recommendations, and vote on a premarket approval application supplement for a new indication for the cobas HPV Test. This device is a qualitative in vitro test for detection of human papillomavirus (HPV) that is currently approved for use in conjunction with cervical cytology.

The proposed new indication for use: In women 25 years and older, the cobas HPV Test can be used as a first-line primary cervical screening test to detect high-risk HPV, including genotyping for 16 and 18. Women who test negative for high-risk HPV types by the cobas HPV Test should be followed up in accordance with the physician's assessment of screening and medical history, other risk factors, and professional guidelines. Women who test positive for HPV genotypes 16 and/or 18 by the cobas HPV

Test should be referred to colposcopy. Women who test high-risk HPV positive and 16/18 negative by the cobas HPV Test (12 other high-risk HPV positive) should be evaluated by cervical cytology to determine the need for referral to colposcopy.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in connection with 18 U.S.C. Section 208.

Glen Freiberg is serving as the Industry Representative, acting on behalf of all related industry, and is president of regulatory affairs and operations for RCQ Consulting.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological

Health, dated October 27, 1990, and as amended August 18, 2006, I appoint the following individuals as voting members of the Microbiology Devices Panel for the duration of this meeting on March 12th, 2014:

George Birdsong, M.D.; Robert Burk, M.D.; Joanna Cain, M.D.; Brent Blumenstein, Ph.D.; Lizzie Harrell, Ph.D.; Paula Hillard, M.D.; L. Stewart Massad, M.D.; Kenneth Noller, M.D.; Kenneth Rand, M.D.; Mona Saraiya, M.D., M.P.H.; Elizabeth Unger, M.D., Ph.D.; Alex Waxman, M.D., M.P.H.

In addition, I appoint Angela Caliendo, M.D., Ph.D., to act as temporary voting chairman for the duration of this meeting.

For the record, these individuals are special Government employees or regular Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at the meeting.

This was signed by Jeffrey Shuren, M.D., J.D., Director of the Center for Devices and Radiological Health, dated March 11, 2014.

Before I turn the meeting back to Dr. Caliendo, I'd like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated, telephone number (410) 974-0947.

Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

Handouts of today's presentation are available at the registration desk.

The press contact for today's meeting is Susan Laine. She will be here later this morning.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you would like to present during today's Open Public Hearing session, please register with Mr. James Clark or Ms. AnnMarie Williams at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and other electronic devices at this time.

Dr. Caliendo.

DR. CALIENDO: We will now proceed to the Sponsor's presentation. I would like the Sponsor to approach the podium.

I will remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

The Sponsor will have 75 minutes to present. You may now

begin your presentation.

DR. MAJEWSKI: Good morning. My name is Christoph Majewski, and I am the lifecycle leader for HPV and microbiology at Roche Molecular Systems in Pleasanton, California.

I would like to thank the Agency for inviting us here today, and the esteemed Panel for joining us to discuss our submission for adding a primary screening claim to our cobas HPV Test. It is a great honor for us to have the opportunity to discuss our data supporting the safety and effectiveness of the cobas HPV Test and the specific indication.

I'm joined this morning by my colleagues and distinguished experts who will present in support of our application. After my brief introduction, Dr. Thomas Wright, Professor Emeritus from Columbia University, will describe the clinical need for an additional option for cervical cancer screening. Dr. Abha Sharma will then briefly familiarize you with the statistical plan of our pivotal study, known as ATHENA. Dr. Catherine Behrens, our Director for Clinical Research, will then share with you the data of the ATHENA study. The data presented will be used to demonstrate the safety and effectiveness of the cobas HPV Test in an HPV-based primary screening algorithm. Dr. Wright will conclude our session with the clinical implications and the favor of risk and benefit for this new indication.

Since the introduction of cervical cytology about 60 years ago, cervical cancer screening is now well established in many countries. For most

of this time, the Pap smear was the exclusive screening test, and that led to a significant reduction in cervical cancer incidence. With recognition that 99% of all cervical cancers are caused by an infection with the high-risk human papillomavirus, HPV testing was introduced as a triage of the clinical cytology and a little later as a co-test with cytology for women 30 years and older. Despite this effort, about 40 women have died almost daily with cervical cancer, and 10 women die daily in the United States. In the U.S., both cytology alone and co-testing with HPV and the Pap test are recommended options for screening of women 30 and above.

While these technologies have led to the lower incidence of cervical cancer screening we're seeing today, they have well-known limitations. Dr. Wright will be discussing those in greater detail later this morning. We believe that offering HPV primary screening as an additional option for screening can address some of these limitations, as we will be showing during our presentation.

We're here today to discuss the addition of an indication for using HPV as a first-line screening test in women 25 years and older for the cobas HPV Test. This indication is currently not included in the consensus guidelines, and it will be up to professional societies and not up to Roche to discuss inclusion of such an option in the future.

We specifically propose that women who are 25 years and above can be tested first with the cobas HPV Test in order to triage them into

the appropriate risk groups as follows:

- Women who test negative for high-risk HPV tests by the cobas HPV Test should be followed up in accordance with physician's assessment of screening and medical history, other risk factors, and professional guidelines.
- Women who test positive for HPV genotype 16 and/or 18 by the cobas HPV Test should be referred to colposcopy.
- Women who test high-risk HPV positive for any of the 12 other high-risk HPV types, but are 16 and 18 negative, should be followed up with cytology to assess the need for colposcopy.

Let's now first have a closer look at how the cobas HPV Test is designed to support the proposed indication.

The cobas HPV Test detects 14 high-risk HPV genotypes, and it reports the HPV results simultaneously. The test runs on the automated cobas 4800 System for PCR amplification and detection, and it provides a pooled result for 12 of the high-risk HPV types, plus individual results for both HPV 16 and HPV 18. The human beta-globin gene target is used as an internal control. This allows the assay to detect a lack of cellular DNA or the presence of inhibitory substances in the sample that could affect the HPV results. This design integrates genotyping for 16 and 18 so that those individual genotypes

are reported simultaneously and not as a follow-up test to a generic high-risk HPV result.

Why did we decide to split out reporting for HPV 16 and 18? There is ample evidence now that these two genotypes are the most aggressive HPV genotypes in terms of cervical cancer development. More than 70% of the squamous cell carcinomas and adenocarcinomas are actually caused by exactly these two genotypes.

It is also well known that genotype 18 is more frequently the cause of adenocarcinomas, which are more difficult to detect with cytology-based screening techniques.

Separate detection of these genotypes provides additional information about the specific disease risk of a woman that may justify different follow-up than the presence of any of the other high-risk HPV genotypes.

The data we are going to present today are based on our pivotal registration study, known as ATHENA. At the outset, Roche wanted to design a study sufficiently robust to support the approval of all current uses of HPV testing, ASC-US triage, and co-testing and to also allow an evaluation of its use in HPV primary screening.

The ATHENA trial is the largest prospective study of cervical cancer screening methods in the United States, enrolling more than 47,000 women in a routine screening setting and including a three-year follow-up of

more than 8,000 women. This large sample size allowed us to evaluate and compare clearly predefined clinical outcomes of various management strategies in a representative U.S. population.

The ASC-US triage and co-testing claims, using data from the cross-sectional part of the study, were approved by the Agency in April 2011. Since then, the cobas HPV Test is marketed in the U.S. for these two indications.

For the PMA supplement and the discussion, our primary objective was to prove the safety and effectiveness of our candidate algorithm, the use of the cobas HPV Test for screening in women 25 and above, to detect precancerous lesions early without compromise to a woman's health or an increase in the number of colposcopies.

I would now like to introduce Dr. Thomas Wright, who will review the clinical need for additional options for cervical cancer screening.

DR. WRIGHT: Good morning. I'm Tom Wright. I am a gynecological pathologist who served as one of the reference pathologists on the ATHENA trial. I also am a consultant to Roche Molecular. I am a past president of the American Society of Colposcopy and Cervical Pathology. And my objective over the next 15 minutes is to explain why we need HPV as a primary screening test in the United States.

For the last 60 years, the primary method of preventing cervical cancer, both in the United States and in Europe, has been cervical cytology. If

the cytology is negative, something we refer to as NILM, or negative for intraepithelial lesion or malignancy, women are rescreened in three years. If the cytology result is abnormal, then a woman is referred to colposcopy. This is a comparator algorithm that Dr. Behrens will use during her presentation of the ATHENA data, and this is considered an acceptable screening approach by both the U.S. Preventive Services Task Force and the American Cancer Society.

As cytology-based screening has continued to evolve, it has become clear that cervical cytology has a number of limitations. The first limitation is that the interpretation of cytologic findings is subjective, and this produces substantial intra- and inter-laboratory variation in how slides are interpreted.

As part of a trial to determine how best to manage women with ASC-US and low SIL, the National Cancer Institute had about 5,000 cytology slides reread by a second cytopathologist. Only 78% of the slides originally classified as negative were considered negative when reviewed by the second cytopathologist. Perhaps even more concerning, only 47% of the slides originally classified as HSIL were diagnosed as high grade on review.

The poor reproducibility of cervical cytology leads to significant inter-laboratory variability. This is nicely shown in an analysis of the ATHENA data that we recently published. Cytology specimens for the ATHENA trial were evaluated in four different College of American Pathologists accredited

laboratories. Patient's age, which is a major factor in the rate of cytological abnormalities, was similar in each of the laboratories. However, when we look at the abnormal rate at these laboratories, it varied considerably, from 3.8% to 9.9%.

Perhaps even more concerning, the sensitivity of cytology at the four laboratories for CIN2 or greater varied from 42% to 73%. In contrast to the variable performance of cytology, the sensitivity of the cobas HPV Test was almost identical across the four laboratories.

The second limitation of cytology is that it has a relatively low and variable sensitivity for the detection of high-grade cervical cancer precursors.

This is a review of the performance of cytology that was done for the U.S. Preventive Services Task Force's 2012 screening guidelines. The sensitivity of a single cervical cytology in the five studies ranged from 44% to 74%, which is almost identical to the range found across the four ATHENA laboratories.

The U.S. Preventive Services Task Force also performed a systematic review comparing the performance of HPV testing with cytology. HPV testing consistently demonstrated a greater sensitivity for CIN2 or greater compared to cytology, with an average increase in sensitivity of 35.7%.

The final limitation I want to talk about of cytology is that it

identifies women with cervical cancer precursors, but it doesn't identify which women will develop high-grade cervical cancer precursors or cancer in the future. In contrast, HPV status is highly predictive of who will develop disease in the future.

This is an NCI study of more 20,000 women who had negative cervical cytology at baseline and were subsequently followed for up to 10 years. Among women who were HPV negative -- the bottom gray line -- almost none developed CIN3 or higher. In contrast, about 20% of HPV 16 positive women and 17% of the HPV 18 positive women developed disease. Women infected with one of the 12 other high-risk HPV genotypes -- that's the green line -- had a much lower risk of developing high-grade disease.

The results of this study, as well as those of many other follow-up studies, clearly documents that HPV status predicts which women will subsequently develop high-grade cervical cancer precursors.

In an effort to overcome the limitations of cytology and take advantage of the higher sensitivity of HPV and its ability to predict who will develop disease, screening using the combination of cytology and HPV was introduced in 2004 for women 30 years and older. This strategy is often called co-testing.

When co-testing, women are screened using both cytology and HPV and then are managed based on the results of both tests. Women with negative cytology who are HPV positive, they can either be retested in 12

months or we can genotype them to determine whether or not HPV 16 or 18 is present. Currently, less than 50% of women in the U.S. appear to be being screened using co-testing. The majority of women in this country are screened using cytology alone.

These are the different diagnostic categories that are used for cervical cytology. Not only do we have NILM, ASC-US, low SIL, and HSIL that we've already spoken about, but we also have atypical squamous cells -- cannot exclude high grade -- four types of glandular abnormalities, and three categories to describe specimen quality. This makes management quite complex. In fact, clinicians now have 12 different management algorithms just for managing cytology results.

This is just one of the 12 algorithms, the one used for women with low SIL. These algorithms have now become so complex that clinicians who do not specialize in cervical disease are actually finding it difficult to utilize them.

Primary HPV screening overcomes many of the limitations of co-testing. We use the first, most sensitive test, HPV first, to determine which women are at greatest risk of having or developing high-grade disease. We then use more specific tests, including genotyping for HPV 16 and 18 and cytology in women who are positive for 12 other high-risk genotypes, to determine who needs colposcopy.

This primary screening algorithm is Roche's candidate

algorithm, and it greatly simplifies how we screen, compared to using either cytology alone or co-testing. And because of its advantages, Roche defined this approach up front as their candidate algorithm.

As we try to simplify how we screen by introducing primary HPV screening, we need to reconsider the age at which we begin HPV testing. Current U.S. screening recommendations do not recommend co-testing for women 25 to 29 years of age. In large part, this is because transient HPV infections are common in this age group, and guideline makers did not want to cause unnecessary follow-up and colposcopy examinations.

However, there is a high burden of CIN3 in this age group, and screening audits from the UK National Health Service have clearly shown that cytology performs poorly in young as opposed to older women.

In 2013, Kaiser Northern California reviewed their registry data, and they decided to extend co-testing to women 25 to 29 years, despite the U.S. screening guidelines.

When considering whether to utilize HPV testing in women 25 to 29 years of age, it is useful to look at the incidence of cervical cancer by age group in the U.S. Data from the NCI SEER tumor registry shows that a sharp rise in the incidence of invasive cervical cancer occurs between ages 25 and 34 years. This suggests that it is very important to identify high-grade cervical cancer precursors in women 25 to 29 years of age so that the precursors can be treated and the subsequent rise in invasive cervical cancer

prevented.

Another factor we need to consider is the prevalence of high-risk HPV in this age group. In ATHENA, 21.1% of women 25 to 29 years of age were high-risk HPV positive. However, the prevalence of HPV 16 and 18 in this age group is much lower. Only 5.3% of women 25 to 29 years of age were HPV 16 positive and 1.6% were HPV 18 positive. In fact, the prevalence of HPV 16 and 18 in this age group is lower than the rate of cytological abnormalities, which was 9.5%.

We also need to consider the prevalence of high-grade disease. Twenty-eight percent of all the CIN3 found in ATHENA was found in women 25 to 29 years of age. There actually is more high-grade disease found in the 6,647 women 25 to 29 years of age than in the 22,000 women 40 years and older.

The final consideration is how the cytology performed for detecting high-grade disease in this age group. In ATHENA, 57.3% of women 25 to 29 years of age with CIN3 or greater had a negative cytology. This is much higher than is seen in women 40 years and older. Because of the high prevalence of disease, the poor sensitivity of cytology in this age group, ATHENA decided to evaluate the performance of primary HPV screening beginning at 25 years of age.

In summary, there are a number of issues that highlight the clinical need for primary HPV screening beginning at age 25. The first is that

cervical cytology appears to have reached the point where it alone is unable to reduce cervical cancer further.

Secondly, management algorithms are extremely complicated, and this is leading to confusion among clinicians.

Finally, cytology appears to be a poor solution for screening women 25 to 29 years of age.

In her talk, Dr. Behrens will present the results of the ATHENA trial that clearly demonstrate the safety and effectiveness of primary HPV screening in women 25 years and older.

Thank you very much.

DR. SHARMA: Good morning. My name is Abha Sharma. I'm the project statistician for the ATHENA clinical trial.

As Dr. Wright pointed out, there is room to improve current cervical cancer screening by using triage strategies that improve detection of women at risk for cervical cancer. To address this need, Roche Molecular Systems designed a clinical study.

The requirements of the study were to design a study with a sufficiently large sample size, to have enough cases of CIN2 or greater with a follow-up to assess the safety. The population needed to be representative of intended-use population, and our design needed to allow for verification bias adjustment; that is, we wanted to be able to assess the performance of the cobas test in all women in the intended-use population.

The objective of the ATHENA study was to compare the HPV-based candidate algorithm to a cytology-based algorithm. Dr. Wright has previously described the predefined candidate and comparator algorithms.

A new algorithm, introduced in 2012, was added to the clinical study report as an additional comparator to reflect current guidelines. This algorithm is called ATRI NM 30GT, in short, and is also referred to as hybrid co-testing in women over 30 years. Comparison with this algorithm is for additional information. The study objective remains what was originally planned, that is, to demonstrate that performance of candidate algorithm is acceptable when compared to cytology.

The study protocol endpoint for algorithm comparisons was CIN2 or greater. We also performed all the analyses with CIN3 or greater endpoint. The conclusions were the same with both of these endpoints. In the results presentation, you will see the data for CIN3 or greater, since it's the better surrogate for cervical cancer.

The algorithms were compared using sensitivity/specificity, positive predictive value/negative predictive value, which helps us look at the risk from a physician and a patient's perspective, and positive likelihood ratio/negative likelihood ratio. The acceptance criteria described here was based on comparing positive likelihood ratio and negative likelihood ratio between the candidate and the comparator.

We used likelihood ratios to assess the performance because

they are independent of prevalence, like sensitivity and specificity, and still have meaning at the per-patient level, like positive and negative predictive values.

A positive likelihood ratio indicates a shift in the probability of favoring the existence of a disease, if the algorithm result is positive. It should be > 1 for a meaningful test so a true positive is more likely than a false positive.

A negative likelihood ratio indicates a shift in probability, favoring the absence of disease, if the algorithm result is negative. It should be < 1 for a meaningful test so a false negative is less likely than a true negative.

Next, we can see how to visualize these parameters. This graphical representation allows us to visually compare the tradeoffs between the two algorithms when an increase in sensitivity is offset by a decrease in specificity. We start with the reference point at the center of the graph, displayed by its sensitivity and 1 minus the specificity. The reference point represents the comparator algorithm. Slope of the black line is PLR, and the slope of the gray line is NLR of the comparator algorithm. These two lines divide the pairs of sensitivity and specificity into four regions.

The algorithm with the estimates in the upper left quadrant are superior because they have higher PLR and lower NLR. It should be noted that high PLR corresponds to high PPV, and lower NLR corresponds to higher

NPV. The algorithms in the lower quadrant are inferior. We used this graph, in addition to quantitative confidence intervals, to help us visualize the comparative algorithm performance.

The performance estimates had to be adjusted for verification bias because, by design, all women with positive results for cytology or HPV were selected for disease verification, but only a random subset of women with double-negative results were invited for disease verification. So we have verified disease by colposcopy in approximately 8,000 women, but we would like to know the disease status of all the evaluable 41,000 women.

To estimate disease, we first correct for how these women are selected. These are adjustment factors by design. We then go one step further, to check that it is acceptable to extrapolate disease within each design subset by verifying that the characteristics of women with unverified disease are the same as women with verified disease or verified the missing-at-random assumption. With the set of selected adjustment factors, we calculate the likely number of disease cases in women without disease verification.

In conclusion, the ATHENA study compared predefined candidate algorithm and comparator algorithm. The statistics were adjusted for verification bias, which allows unbiased assessment of algorithm performance. The candidate was considered better than comparator. The negative likelihood ratio is smaller and positive likelihood ratio is larger than

the comparator. We also calculated three-year cumulative risk for a negative HPV result to show the safety over three years.

Thank you for your attention. Dr. Behrens will now present the results of the study.

DR. BEHRENS: Good morning. I'm Catherine Behrens. And thank you for the opportunity to present our data in support of HPV testing as a first-line primary screen for cervical cancer. Today I'm speaking in my role as Clinical Research Director at Roche, but I've also been a board certified OB/GYN for more than 20 years, so I'm also speaking as a longstanding advocate for women's healthcare.

Now, Dr. Wright has so clearly defined the challenges that were faced at the beginning of the ATHENA trial. Can we improve existing methodology, and can we add medical value to cervical cancer screening by increasing the effectiveness of disease detection?

By way of background, as you have heard, the ATHENA trial is the largest prospective cervical cancer screening study conducted in the U.S. to date. During the course of the study, more than 47,000 women, 21 years and older, were enrolled at 61 sites across 23 states, and 4 clinical laboratories were enlisted for testing.

The ATHENA study served as the registrational trial for the cobas HPV Test with 16/18 genotyping, and based on the cross-sectional data, FDA approval was granted in 2011. Today, the approved intended uses are

for the management of borderline or ASC-US cytology results and also as an adjunctive test to cytology. The data that we will present today will be to support the additional claim of HPV as the primary screening test.

At the outset, the ATHENA trial was specifically designed so that it could demonstrate the performance of HPV testing and cervical cancer screening in the United States. To achieve this objective, first the ATHENA population had to be representative of a U.S. screening population. Secondly, the study design had to allow for all women to have both cytology and HPV testing at enrollment. And most importantly, to be able to compare the performance of HPV testing to cytology, all women with either abnormal cytology or positive HPV results had to be referred for colposcopy. Colposcopy was performed by protocol, and a histologic diagnosis of all biopsies was determined by the consensus review of expert pathologists.

On the next several slides we will show how the ATHENA population was representative of a U.S. screening population, in terms of the demographics and the baseline epidemiology of both cytology distribution and HPV prevalence.

And I should mention that although the trial enrolled women 21 years and older, the data that we will be showing today is from what we would propose as an HPV primary screening population, women 25 years and older.

On the first slide of this series we see that the median age of

the ATHENA population was 41 years, and approximately 83% of the women were white, 14% African American, and 2% Asian; 18% declared themselves to be Hispanic. And we can also see that these numbers are reflective of the U.S. population, falling within the range of figures from the 2012 census.

Cytology for the ATHENA study was performed at four high-volume accredited labs located in the U.S. If we look at the distribution of cytology results in ATHENA, we see again that the observed distribution was what would be expected in a U.S. screening population when compared to the 50th percentile results of the CAP survey. And of note, the CAP numbers are not adjusted for women 25 years and older.

Now, in terms of HPV prevalence, 10.5% of the women 25 years and older in ATHENA were found to be HPV positive, and when stratified by genotype, 2.1% were HPV 16 positive and 0.8% were HPV 18 positive. If we compare these prevalences in ATHENA to the cohort from the New Mexico HPV Pap Registry, the only recognized cervical cancer registry in the U.S., we see slightly higher values, but relatively close agreement.

There were also some minor differences in the genotypes considered oncogenic in these two studies, and that might account for some of the small discrepancies. In the overall New Mexico cohort we see 14.2% HPV positive, 3.1% HPV 16 positive, and 0.9% HPV 18 positive. As expected, in the ATHENA population we saw the HPV prevalence decrease with age, and likewise a similar decrease was seen in the New Mexico registry.

Now, the next two slides will show the design of the ATHENA trial in more detail. This first slide shows the patient flow for the cross-sectional phase of the study that was designed to demonstrate the effectiveness of HPV testing for cervical cancer screening. This phase of the study took place from 2008 to 2009, during which time over 42,000 women 25 years and older were enrolled. Again, at enrollment, women had both liquid-based cytology with ThinPrep and HPV testing performed, and the results were used to determine referral to colposcopy.

As you can see on the right side of the chart, all women with abnormal cytology, ASC-US or greater, and all women with positive HPV results proceeded to colposcopy. And on the left side, women with negative cytology and negative HPV results exited the study after the enrollment visit, except for a subset of approximately 1,000 with negative/negative results who were randomized to colposcopy so that verification bias adjusted statistics could be estimated.

In total, approximately 8,000 women were taken to colposcopy and biopsy, and those who reached the study endpoint of CIN2 or greater were eligible for treatment and then exited the study. Those who did not reach the study endpoint of CIN2 or greater were invited to participate in the follow-up phase of the study, which concluded in 2012 and which provided sufficient follow-up to determine the safety of screening.

Of the approximate 8,000 eligible for follow-up, 1359 exited

and did not proceed to follow-up. And during follow-up, women were seen annually and had both cytology and HPV testing performed, and only women with abnormal cytology, ASC-US or greater, were referred to colposcopy and biopsy. As in the baseline phase, those who met the endpoint of CIN2 or greater exited the study, and those with less than CIN2 proceeded to the following year. And at Year 3, all women were offered an exit colposcopy.

Now that we have looked at the ATHENA population and study design, let's take a few moments to review some of the terminology generally used in managing the results from cervical cancer screening procedures, for those who may not be familiar with them.

For cytology, the Bethesda classification is used, and Dr. Wright has already reviewed the various categories. The management of these cytology categories is also defined. Negative Paps are managed by routine follow-up, which is now three years. ASC-US is managed either by repeat testing in one year or triaging with HPV testing. The remainder of the cytology categories are all considered screen positives and are all referred to colposcopy.

As most of you know, colposcopy is a procedure where the clinician uses a colposcope to magnify the cervix, and if abnormal areas are seen, a biopsy is taken to determine if pre-cancer or cancer is present. The histology of these biopsies can be classified as negative, cervical intraepithelial neoplasia Grade 1, or CIN1, then CIN2, CIN3, adenocarcinoma

in situ, or invasive cancer.

The biopsies outlined here in orange are classified as CIN2 or greater and those in blue as CIN3 or greater. Histologic results of CIN2 or greater are considered pre-cancer, and in the past CIN2 or greater has been the threshold for treatment. However, CIN3 or greater has more recently been considered a better surrogate for cancer when assessing screening strategies, and this was emphasized in the 2012 guidelines.

And so for this reason, when we present data on the performance of the various strategies today, we will be presenting data only for CIN3 or greater, but we would be happy to share the data that we have for CIN2 or greater with anyone who has a preference for that endpoint.

Now, in the introductory remarks, Dr. Wright reviewed data demonstrating the increased oncogenicity of HPV 16 and 18, placing women infected with these genotypes at highest risk for pre-cancer. We also saw that the cobas HPV Test is technically able to report out a pool of 12 other high-risk genotypes as well as HPV 16 and 18 individually.

And so this slide illustrates that the cobas HPV Test can successfully predict risk for high-grade disease when stratified by genotype. This is particularly important since the ability to detect 16/18 disease will play a key role in our algorithm for HPV primary screening.

We show here the three-year cumulative risks from enrollment through the longitudinal phase of ATHENA for CIN3 or greater, a stage of the

disease unlikely to regress. And these risks are stratified further by genotype as would be reported out by the cobas HPV Test result. We can see that the higher risks associated with HPV 16 and 18 were confirmed in our study at baseline and over the three-year follow-up. In fact, in the overall population of women 25 years and older, those who are HPV 16 positive at baseline have a risk of being diagnosed with CIN3 or greater of approximately 25% at three years. And likewise, the risk for those HPV 18 positive at baseline is approximately 10%, and this was greater than the risk for all the other pooled high-risk HPV genotypes together.

And of note, most of the HPV-associated disease was detected at baseline, with little additional disease seen over the three years. And it's also worth noting the low risk of CIN3 or greater over the three years in those women who tested negative for HPV at baseline. And we will see these numbers expanded in a slide to come.

Now, we've covered a lot of background information, but with this information we can now go forward and discuss the various screening algorithms.

The recent joint guidelines for cervical cancer screening that were issued in 2012 stressed the importance of balancing the benefits of screening, that is, the detection of disease against the harms of screening. From a clinical perspective, potential harms of colposcopy for patients include discomfort from the procedure and also the anxiety brought on by

undergoing a procedure that they had never had before and the possibility of being diagnosed with a pre-cancerous condition.

But when assessing the harms of screening over and above the harms of colposcopy, we must also consider the very real harm that can result from pre-cancer that is missed by cytology, perhaps as much as 40% of CIN2 or greater not detected on the Pap smear, as Dr. Wright discussed in his remarks.

And, of course, the other side of that coin is over-management, in the form of extra follow-up clinic visits, and ultimately over-treatment of lesions likely to regress. We also know that the lesions detected with colposcopy can result in treatment by surgical excision, which may lead to longer-term complications related to pregnancy, most notably the tendency toward pre-term labor and delivery brought on by the surgically weakened cervix.

So when determining the optimal screening strategy, the sensitivity, or the maximum disease detection, has to be weighed against the specificity, or the risk of over-management and over-treatment.

Now, just to refresh your memory, the data on the performance of the various screening algorithms that we will be showing over the next several slides will be based on the cross-sectional results, these approximately 8,000 women who were triaged to colposcopy in the baseline phase of the ATHENA study.

Now, as you can image, there are many algorithms with various combinations of cytology and HPV testing that could be constructed from these data. But today we will focus on the HPV primary screening strategy that has the most potential to improve screening, and this will be referred to as the candidate strategy.

The performance of this candidate algorithm will then be compared to two comparators. The first will be cytology alone, since it is an option for screening that is supported by current guidelines. Cytology alone, referred to as the comparator, also reflects longstanding clinical practice and represents the minimal threshold for acceptable clinical performance for determining safety and effectiveness.

The additional comparator will be a co-testing strategy that is also endorsed by current guidelines, formally referred to as ATRI NM 30GT and informally as the co-testing hybrid. In this algorithm, women 25 to 29 years are screened with a cytology-based strategy only, and women 30 years and older are screened with both cytology and HPV, or co-testing.

To demonstrate effectiveness, each screening algorithm will be evaluated by comparing the sensitivity and specificity to detect pre-cancer, as well as the predictive values and likelihood ratios. To demonstrate safety, the negative predictive value will be evaluated. And, additionally, the three-year cumulative risks, or CIRs, for a negative HPV result versus a negative cytology result at baseline will also be calculated and compared. And as mentioned

previously, only data using CIN3 or greater as an endpoint will be presented, since it is considered a better surrogate for cervical cancer when assessing screening strategies.

The first algorithm is the comparator, cytology alone. As Dr. Wright described, in this strategy, Pap alone is performed, and a woman who tests negative would be referred back to routine screening, while those ASC-US or greater would be referred to colposcopy.

The second algorithm is the candidate algorithm. This is an HPV-based strategy that Dr. Wright introduced, where HPV with genotyping is the first-line test, and women who test positive for HPV 16 or HPV 18 are referred to immediate colposcopy. Those who test positive for a pool of 12 other, or the non-16/18 genotypes, have cytology performed, and those with an ASC-US or greater result are referred to colposcopy.

This next slide is the first in a series that will build a table comparing the verification bias adjusted sensitivity and specificity relative to the comparator, cytology alone, for detection of CIN3 or greater in women 25 years and older for each of the algorithms.

Here we see that the sensitivity of the candidate algorithm relative to the comparator is 1.37, indicating an increase of 37% over cytology in the detection of CIN3 or greater. We can also note that the specificity of the candidate is now equal to and actually superior to cytology. So we see that we have increased the sensitivity to detect high-grade disease by using

an HPV-based strategy, and we have increased the specificity of HPV by adding 16/18 genotyping and reflex cytology.

In this next slide we show the comparison of the predictive values and likelihood ratios of the comparator and the candidate algorithms. We see that for the detection of CIN3 or greater, the positive predictive value, or the PPV, of the candidate strategy is approximately 12% and nearly two times that of cytology alone, meaning that if we take all screen-positive women to colposcopy, two times the number of women who screened positive with the candidate strategy will be found to have pre-cancer on colposcopy compared to those who screened positive with cytology.

Likewise, in the second to last column, the increase in the candidate PLR tells us that, for women who screen positive, the odds of having CIN3 or greater increased approximately 14-fold over what would be the expected prevalence. On the other hand, the odds only increased by a factor of seven for those who screen positive with the comparator. These improved performance parameters speak to an improved measure of effectiveness for the candidate strategy.

We also see that the NPV is slightly, but significantly, increased with the candidate algorithm, and this means that women who test negative with this strategy can be given more reassurance that they don't have high-grade disease than women who screen negative with cytology. We see the same result for the candidate NLR, which predicts lower odds of having

disease when screening negative than with the comparator. And so we see that safety has also been improved with the candidate strategy.

To summarize, all performance parameters met the study objectives, as described by Dr. Sharma.

The next algorithm is the second of the strategies supported by the current guidelines. In this co-testing hybrid strategy, women 25 to 29 years are screened with cytology only, while women 30 years and older undergo co-testing with both cytology and HPV. Now, this strategy will look complicated, and for many clinicians, it is complicated. But nonetheless it's the strategy supported by the current guidelines. For the sake of clarity, this algorithm will be described in two slides.

Here in this first slide we start with ASC-US triage for women between ages 25 to 29. In the second part of the co-testing hybrid, HPV testing is added to cytology for women 30 years and older, and the combination of cytology and HPV results is used to triage to colposcopy.

To review briefly what Dr. Wright has already described, women who are ASC-US HPV positive or greater than ASC-US are referred to colposcopy. For women with negative cytology who are HPV positive, only those HPV 16 or 18 positive are referred to colposcopy. And those testing positive for the non-16/18 12 other genotypes are followed up in 12 months.

When we look at the sensitivity and specificity, we see that the sensitivity of this additional comparator to detect CIN3 or greater actually

decreases when compared to the candidate. The reason for this decrease is that women 25 to 29 are only screened with the less sensitive cytology strategy and significant disease is missed. However, specificity remains unchanged.

As for the predictive values, the PPV for CIN3 or greater for the candidate is nearly 12% compared to 11% for the co-testing hybrid, and this is a statistically significant difference. The PLR is also increased, predicting a higher likelihood of disease when screening positive for the candidate versus the co-testing hybrid. The NPV and NLR are also slightly, but significantly, improved for the candidate. And so, again, screening with the candidate algorithm would result in improved safety and effectiveness over the existing guideline-supported strategy.

Now, sometimes it's easier to just see these comparisons graphically. Dr. Sharma has already introduced this type of data presentation, so we can see in this slide that we have used cytology as the comparator and plotted the point estimates for sensitivity and 1 minus specificity, or a false positive rate, for detection of CIN3 or greater.

If we draw a line from the .00 through the point estimate, the slope of the line represents the positive likelihood ratio of cytology. Likewise, if a line is drawn through the point estimate and extended to the .11, the slope of this line is the negative likelihood ratio of the comparator. We'll now focus on the area within the orange rectangle and enlarge that portion of the

graph.

Again, we plot the point estimates for the comparator and add in the lines representing the slopes of the PLR and NLR. This now defines four quadrants which describe the performance of a test. Tests falling in the left upper quadrant have improved PLR and improved NLR. We can easily see that the candidate and the co-testing hybrid algorithms both show superior performance when compared to cytology. And if we look at this graph as an ROC-like curve, we see that the candidate strategy, occupying the left upper most position, offers the best balance of sensitivity and specificity.

Now, in addition to exploring performance parameters, we also wanted to evaluate how these algorithms would function in a clinical situation. So we calculated a series of variables to determine how well the clinical management of each strategy is balanced.

In this table, for the three strategies, we'll compare the number of screening tests that would be required to implement each strategy, the number of screening tests performed for each disease case detected, the number of colposcopies, the number of colposcopies that would need to be performed for every disease case detected, which is the surrogate for specificity, and the total number of disease cases detected, or the sensitivity.

For the comparator, cytology, 40,944 initial tests would need to be performed. By comparison, the candidate requires slightly more first-line screening tests, but as you can see in the next column, a lower ratio of tests

to disease is required, approximately 190 to 240. In addition, the candidate algorithm proves to be the more efficient strategy by having the lower ratio of colposcopies, 8.1, needed to detect one disease case, as compared to the comparator with 15.3. And, again, the candidate demonstrates higher sensitivity by detecting an increased number of CIN3 or greater cases, 232, as we can see in the last column.

When the candidate algorithm is compared to the co-testing hybrid, as expected, the number of initial screening tests nearly doubles by co-testing and the number of colposcopies increases, as does the ratio of colposcopies, to 9.1 for each CIN3 or greater case detected. And in the end, the sensitivity is inferior to the candidate, since only 211 cases are detected.

We have reviewed a large amount of data, so let's take a few moments to summarize what we have seen so far regarding the comparison of effectiveness of the candidate to detect disease, and the comparators.

First, the candidate demonstrates the best sensitivity for detection of CIN3 or greater. The specificity of the candidate is made equivalent to cytology when 16/18 genotyping and reflex cytology are added to HPV as the primary screen. The candidate PPV is two times that of cytology and significantly greater than co-testing. And the NPV of the candidate is improved over both cytology and co-testing, as well. And in addition, the candidate demonstrates a better clinical resource utilization profile than either cytology or the co-testing hybrid.

Let's now focus more specifically on the safety of HPV testing. And for this we will look at additional longitudinal data.

Now, we have spent most of this presentation discussing how to triage women who test positive for HPV, when in fact 90% will test negative in a screening population. On this slide we can compare the performance of cytology versus HPV in these 90%.

Here we see the cumulative risk of CIN3 or greater over three years of a negative HPV test at baseline -- and that's the lower curve in gray -- versus a negative Pap at baseline -- the upper curve in orange. The three-year risk for a negative baseline HPV result is 0.34% compared to 0.78% for a negative Pap at baseline. So, in fact, the risk of being diagnosed with CIN3 or greater over the three-year period for a woman with a negative HPV result is one-half the risk predicted by a negative Pap.

And so for a clinician, if only one test could be performed over a three-year period, the choice should be straightforward. Clearly, the lower risk associated with a negative HPV result provides more reassurance to both patient and clinician that disease will not be diagnosed over the next three years. And the lower risk for developing CIN3 or greater over three years for HPV also confirms the safety of a negative HPV test for a three-year interval.

Now, for the sake of completeness, we can also look at what the risk would be in a screening population of women 25 years and older for pure co-testing, not the hybrid.

In this graph we see that the addition of a negative Pap to a negative HPV result at baseline -- the bottom orange curve -- lowers the risk of being diagnosed with high-grade disease slightly over three years, but the benefit is marginal. And keep in mind that this is co-testing at age 25, and it is more than is done in practice today, and the benefit is still marginal. In addition, co-testing comes at the expense of increasing the rate colposcopy from 4.6% for the candidate to 5.4% for co-testing.

Now, although the goal of screening is to prevent cervical cancer, not diagnose it, we also looked at the ability of HPV to detect invasive cancers. And since we only detected eight cancers in the ATHENA study, we were able to obtain additional samples from the University of New Mexico HPV Pap Registry that were collected in liquid-based cytology from women subsequently diagnosed with cervical cancer.

We see here that in the ATHENA cohort, all cases were cobas HPV positive, and of note, one was cytology negative. In the New Mexico cohort, two cases were cobas HPV negative. But after HPV testing was completed, one of these cases was noted to be an endometrial cancer that was sent in error, and this was not included in the analysis. The other HPV New Mexico case that was cobas HPV negative was an undifferentiated adenocarcinoma with uncertain origin, endocervical versus endometrial. And this would not be expected to be HPV positive if in fact it was an endometrial primary.

In all, the sensitivity of HPV to detect invasive cancer was 96.2%, and it can be argued that it would 100% if the uncertain origin case were excluded.

Again, we have reviewed a large amount of data today, and so it would be helpful to consider the main conclusions that demonstrate the safety and effectiveness of the candidate for HPV primary screening.

First, in general, HPV-based strategies for primary screening are more sensitive for detection of high-grade disease than cytology-based strategies. And the specificity of HPV strategies can be increased by the addition of 16/18 genotyping and reflex testing to cytology.

The effectiveness of the algorithm using the cobas HPV Test with genotyping and reflex to cytology of the candidate is demonstrated by its superior performance compared to the strategies supported by current guidelines, cytology alone and the co-testing hybrid. For the detection of pre-cancer, the candidate provides the optimal balance of benefits and harms.

And, finally, the safety of the cobas HPV Test as a primary screening test is confirmed by demonstrating that a negative HPV result at baseline predicts a lower risk of CIN3 or greater at three years than a negative Pap result at baseline.

Thank you for your attention. And I would now like to reintroduce Dr. Wright, who will address some additional clinical implications.

DR. WRIGHT: Tom Wright again.

What you've just heard this morning is a milestone in U.S. cervical cancer prevention efforts. Not only is ATHENA the largest U.S. screening study, but methodologically it is one of the most rigorous cervical cancer screening studies ever conducted.

I would now like to spend a few minutes discussing the clinical implications of primary HPV screening.

The first clinical implication is that screening for other cancers such as endometrial or ovarian, as well as screening for sexually transmitted infections, will not be adversely impacted if we use primary HPV screening. The sensitivity of cervical cytology for detecting either endometrial or ovarian cancer is relatively low. Depending on the study, only 10% to 30% of women with endometrial or ovarian cancer will have a positive cervical cytology. Moreover, a positive cervical cytology is associated with high-stage disease. Therefore, detecting endometrial or ovarian cancer by cytology does not actually improve a patient's survival. Because of this, cervical cytology is not considered a screening test for other gynecologic cancers by any organization or society.

The same can be said for sexually transmitted infections. Although a number of organisms can be identified by cervical cytology, the sensitivity of cytology is too low to be considered a screening test for these infectious agents by guideline groups such as the CDC or ACOG. It should also

be emphasized that there are other widely available tests that are both more sensitive and more specific for these infectious organisms.

The second clinical implication I would like to address is that shifting from cytology to primary HPV screening will not put women at increased risk for either invasive cervical cancer or high-grade cervical cancer precursors.

When we talk about the sensitivity of any screening test, it is critical to stress that no screening test will detect all CIN3 lesions or cancers. There are a number of reasons for this. They include occasional sampling issues, the rare types of cervical cancer that may not be caused by HPV. When considering the performance of a screening test for cervical cancer, it is important to recognize that since cervical cancer is relatively uncommon, it is actually difficult to determine a test performance. Anecdotal cases or small series of cervical cancers are not informative, and the only accurate approach to evaluating the performance of any screening test for cervical cancer is to use registry data or long-term follow-up studies.

There have been four relatively recent large cervical cancer registry studies. These studies reviewed the screening histories of all women reported to the registries with invasive cervical cancer, and in all four it was found that between one-quarter and one-third of women with invasive cervical cancer had had a negative cervical cytology within the recommended screening interval. This indicates that there are a significant number of false

negative cytology results in women with cancer.

The cancer registry data, shown in the previous slide, fits quite nicely with a more recent review of the screening histories of all women in Kaiser Northern California who were diagnosed with invasive cervical cancer between 2003 and 2010. This review included the screening histories of almost one million women 30 years and older; 20.7% of women with invasive squamous cell carcinoma and 45.6% of women with adenocarcinoma had had a recent negative cervical cytology.

Turning from the performance of cytology to the performance of HPV testing, we now have evidence that HPV testing reduces the incidence of invasive cervical cancer compared to cytology. Pooled data from four European randomized screening trials has recently been published. The pooled data includes 176,000 women 20 to 64 years of age and over 1.2 million person-years of follow-up. One of these trials, the largest from Italy, directly compared HPV screening with screening using liquid-based cytology alone. The other three trials compared co-testing to cervical cytology, but they were able to separate the performance of HPV from that of the cervical cytology.

Between two and three years after screening, there begins to be an increase of the detection of invasive cervical cancer in women who were cytology negative -- the red line -- versus the women who were HPV negative -- the blue line -- clearly demonstrating that HPV testing prevents

more cervical cancers than does cytology.

There is also a considerable amount of data documenting that primary HPV screening would be more effective than cytology for preventing subsequent development of high-grade CIN.

Here we can see the risk of CIN3 or greater stratified by screening test result after three years of follow-up, both in ATHENA and three other studies. The study of Dillner is from Scandinavia, Katki's is from the U.S., and Rijkaart is from the Netherlands. In all four studies there is a lower risk of CIN3 or greater in HPV-negative women than in cytology negative women. Moreover, in all four studies, the level of additional protection provided by co-testing, as opposed to HPV testing alone, is minimal.

The higher risk of CIN3 or greater observed in ATHENA compared to the other studies is most likely due to the fact that in ATHENA, all HPV positive and cytology positive women had an entry and an exit colposcopy performed.

I would now like to turn to the Kaiser Northern California screening registry data that was used in the development of the 2012 American Cancer Society screening guidelines.

Between 2003 and 2005, over 300,000 women 30 years and older were tested in Kaiser with both HPV and cervical cytology. The incidence of CIN3 or greater at three years in women who are cytology negative -- the yellow line -- is the same as the incidence at five years in

women who were negative by both cytology and HPV. This is why the 2012 screening guidelines set the screening interval at three years when using cytology and five years when using co-testing.

For comparison, in the Kaiser data, the risk of CIN3 or greater at three years in women who are HPV negative -- the gray line -- is considerably lower than that for cytology at three years or co-testing at five years. Based on the Kaiser registry data, primary HPV testing at a three-year interval would afford women more protection than either cervical cytology performed at a three-year interval or co-testing performed at a five-year interval.

The clinical implications, I think, of primary HPV screening are clear. First, screening with HPV alone will not adversely impact women with other gynecological cancers or sexually transmitted infections. Second, it is important to point out that no screening test with an acceptable level of specificity will detect all cervical cancers or high-grade precursors.

Although I am sure you have all seen anecdotal cases of cervical cancers that were missed by HPV testing, this morning we have presented registry data and long-term follow-up studies clearly documenting that primary HPV screening offers a greater level of protection against CIN3 and invasive cervical cancer than does cytology when used alone, and this is widely used in the United States today. Moreover, the same long-term follow-up studies and registry data clearly demonstrate that primary HPV

screening will offer a similar level of protection as does co-testing.

Primary HPV screening with triage of HPV-positive women using the candidate algorithm that is shown here detects a significant number of CIN3 or greater lesions that are simply missed using cervical cytology. This means there is a simple, efficient option for the tens of millions of women in the U.S. who today are only being screened with cytology alone. The increased sensitivity of the candidate algorithm compared to cytology is especially important in women 25 to 29 years of age. This is the age group that has the highest burden of CIN3.

It should be stressed that the increased detection of CIN3 or greater that is provided by the candidate algorithm does not come associated with new risks.

Finally, one of the major benefits of primary HPV testing is that it has a potential to greatly simplify screening algorithms compared to screening which is based on cytology.

Thank you very much for your time.

DR. MAJEWSKI: I'd like to thank you all for your attention this morning. This is Christoph Majewski again.

We believe that the data we have presented demonstrates that the cobas HPV Test can improve cervical cancer screening methods when used as a primary test. We have presented a significant amount of complex data, so in closing, allow me briefly to recap.

We're here today to discuss the safety and effectiveness of the cobas HPV Test for use in an additional indication, HPV primary screening in women 25 years and older. We have shown you data that, compared to cytology alone, the cobas test as a primary screening test provides better negative predictive value and negative likelihood ratio, proving the safety of this test. This means that a woman with no CIN3 lesions is more likely to have a negative cobas test result than a negative cytology result.

We have also shown that the cobas HPV Test is superior in identifying women with underlying pre-cancerous lesions of CIN3+, as indicated by better positive predictive value and better positive likelihood ratio, proving the effectiveness with regard to detecting pre-cancerous lesions. Again, this means that a woman with a CIN3+ lesion is more likely to have a cobas positive result than a positive cytology result.

Of note is the performance of the candidate in the age group 25 to 29, where the candidate detected 50% more disease than the comparator, while only marginally increasing the number of colposcopies.

The candidate is also comparable to ASC-US triage and co-testing, the second algorithm currently endorsed by guidelines and all relevant criteria. The three-year cumulative incidence rate of the candidate is about half that of a negative cytology test, and it is very comparable to that of a double-negative co-test.

Finally, the cobas HPV Test demonstrates a well-balanced

benefit and risk ratio, with the number of tests being at the lower end of the spectrum and the ratio of colposcopies actually being best.

In summary, we have shown that by these criteria, the new claim is clearly superior to cytology alone. It introduces no new risks and in fact reduces the number of colposcopies. As the proposed use has been shown to be both safe and effective, we believe it should be considered as an alternative option to the currently approved indication of ASC-US triage and co-testing.

Thank you very much for your attention. We are open to answering any questions you might have for clarification.

DR. CALIENDO: So I would like to thank the Sponsor for their presentation.

Does anyone on the Panel have any brief clarifying questions for the Sponsor? I want to remind you that you will also have an opportunity to ask the Sponsor questions during the Panel Deliberation session this afternoon. So questions? And please remember to introduce yourself when you speak.

DR. WAXMAN: Alan Waxman.

My understanding of the clinical and laboratory flow of this test is that the cobas test, with this indication, will still be used by collecting the sample from the cervix, sending it in a ThinPrep medium; is that correct?

DR. MAJEWSKI: That is correct.

DR. WAXMAN: Okay, so that if reflex cytology, for instance, were indicated, as your algorithm notes, the patient doesn't have to return for another visit. The laboratory could potentially hold on to the vial.

DR. MAJEWSKI: That would be correct, as long as a pre-quot is taken for testing with the HPV from that cytology sample.

DR. MASSAD: I think I know the answer to this, but just to be clear, is this intended for single use, once in a woman's lifetime, or for serial use across time?

DR. MAJEWSKI: So the ultimate uses interval will be determined by professional societies. It's not up for Roche to determine that. What we have shown is, basically, that it is safe to use the test over a three-year interval, repeatedly.

DR. MASSAD: Okay, but there are not data on safety or effectiveness in repeated screening?

DR. MAJEWSKI: No, we don't have that.

DR. MASSAD: Okay.

DR. CALIENDO: This is Angie Caliendo.

My question is, how common is HPV-negative cervical cancer? And are there any data comparing the performance of this assay with other molecular assays in that population?

DR. MAJEWSKI: So that's actually a twofold question. Please allow me to clarify. One is basically, how common is HPV-negative cancer,

and will that affect all of the assays? Is that really your question? We would like to ask one of our clinicians to come up to answer that question.

Tom.

DR. WRIGHT: Tom Wright.

HPV-negative cervical cancer does exist. It is uncommon, most people believe. There is a separate issue of how often does an HPV test be negative in a patient with cervical cancer. Slide up.

These are the studies, which we have, which use a liquid-based cytology specimen. Three of these you have already seen this morning, the ATHENA, the University of New Mexico trial, and Cape Town study. Three of these used hybrid capture 2. One of them was a screening study from China. This was women, 12,000 women, undergoing screening. They had 30 cancers. They used the PCR method. In all of these it's running somewhere between 93% and 94%, is kind of where it looks. Some will be up to 100.

There are a number of reasons, though, when you look at why people have negative cervical cancer. Slide up. This is a study from Germany where they took 92 referred cervical cancers, took a collection, ThinPrep media, and did HPV testing on it, and what they showed was that out of the 92, 85 were positive and 7 were hybrid capture 2 negative.

However, when they looked in the hybrid capture 2 negative cases, like we saw in the ATHENA data, they found there were good explanations for why they were negative. Two were definite endometrial

primaries. There was no question by the pathologist on review. One appears to have been an ovarian primary. It was widely metastatic and involved the ovary. They did immunohistochemistry and it stained like an ovarian cancer. One was probably a bladder cancer, and three were patients who had been referred and who had previously had conizations or LEEP procedures, and on the hysterectomy specimens that they did, they found no residual disease.

So there clearly are going to be HPV-negative cancers. Most people feel they're relatively uncommon.

DR. CALIENDO: Angie Caliendo.

So in follow-up to the second part, is there any difference in the performance of the cobas test in these patients than other tests? You mentioned the hybrid capture.

DR. WRIGHT: I don't think we have enough comparative data to answer that.

DR. CALIENDO: Other questions from the Panel? Go ahead.

DR. SARAIYA: Mona Saraiya.

I had a question on the demographic population. You have just an upper age of 50 and over. Can you talk about the upper age limit and comment on anybody older than 60 or 70?

DR. MAJEWSKI: Your question was specifically about the upper age limit in our data. So there was no upper age limit. So women were enrolled without upper age limit. If you're specifically interested in the

performance in the older patient group, I would ask Dr. Behrens to comment on that.

DR. BEHRENS: Catherine Behrens.

As Dr. Majewski said, there was no upper age limit, and we had women over the age of 65 comprised only about 2.9% of the population, and I believe the number was approximately 30% were postmenopausal.

DR. SARAIYA: Okay, thank you.

DR. CAIN: Joanna Cain.

In your presentation you make a case for improvements over cytology alone, and yet, in your algorithm, you use it as a triage for high-risk non-16/18 HPV positive. Given that cytology is heavily influenced by the experience of pathologists and with this algorithm that experience would drop, how do you justify that use within the algorithm?

DR. MAJEWSKI: I would like to ask Dr. Wright to come up and answer that question.

DR. WRIGHT: Dr. Behrens showed the data.

DR. MAJEWSKI: Okay, please.

DR. BEHRENS: Catherine Behrens.

Yes, thank you. We wanted to see that same information, so we ran a post hoc study unblinding some of the cytology to send back to the same lab and repeat the reading and see what we were able to find. For the candidate, we saw that there was an increase of approximately 5% in the

sensitivity, and that came from the knowledge of the HPV result, as you said, in the 12 other HPV samples. The specificity decreased slightly to approximately .5%, and that increased the colposcopy rate again slightly, from about 4.6% to 5.1%.

DR. CALIENDO: Angie Caliendo.

I think the question, as I understood it, was it's not so much that the person now doing the cytology knows the HPV results. But if we do that much less cytology, what will happen to the competence of the people doing the cytology? Is that correct?

DR. CAIN: Yes.

DR. CALIENDO: And so I don't know if you have any data or anything to answer that.

DR. MAJEWSKI: So the specific question really is, if cytology is actually less frequent, so how would we make sure that the performance doesn't decrease? So I'm going to ask Dr. Wright to comment.

DR. WRIGHT: Tom Wright.

I thought you would like to see the data. Sorry, I didn't address it directly. Clearly, what we are doing is we will be making cytology much more of a diagnostic test than a screening test because it will get them lower numbers. My firm belief, but this is only my belief -- I don't know the data on this -- is that as we have fewer slides to screen, we will actually perform much better. Many of the errors in screening are errors where we just simply miss

things. If technicians had fewer slides, more time to screen to them, more went to the pathologist, I personally believe that there would be better accuracy.

MR. FREIBERG: Glen Freiberg.

We touched a moment ago on the high end of the age range. I'm kind of curious about the low end of the age range. When you began your presentation you said that enrollment included women 21 and above, and yet our indication for use is 25 and above. Without changing a proposed indication for use of 25, so that the clinicians would have all the information from the trial, would there be any problem in requesting FDA to allow you to put a table in the package insert covering the results from the 21 to 25 so that it would all be out there?

DR. MAJEWSKI: So the specific question is whether we would mind to have an exclusion in the package insert -- or have the data in the package insert for the age group 21 to 25. No, of course not. So these data are available, so there's obviously logical reasons why we didn't pursue that for the primary screening indications, because of the very high prevalence in these younger women. But there's no objection against including that.

DR. HARRELL: Lizzie Harrell.

You mentioned that the current cancer screening guidelines are so complex for cervical cancer. Assuming that this test were approved, how do you get the professional societies that are going to be using this test to

buy into it?

DR. MAJEWSKI: Yes. So I think this is basically a question about education; is that correct? How would we basically make sure that information becomes known to everybody?

DR. HARRELL: And will they do it, decide to use it, even if it gets approved?

DR. MAJEWSKI: Yes. So I would ask, as a clinician, Dr. Wright to comment on that piece.

DR. WRIGHT: Professional societies will look at the data. They will make judgments based both on the ATHENA trial data as well as other data, to how they feel this test should best be used. I think there's a lot of education which is being done by many groups. CDC is doing education. There's lots of education available. Whether or not a clinician decides to use this test over using co-testing is clearly the clinician's decision and the professional societies when they make their guidelines. We are not asking that any test be removed. We are not asking that cytology no longer be approved, that co-testing not be available. This would just be another, a third option, for screening.

Thank you.

DR. BURK: Robbie Burk.

Thank you for a very clear presentation. We've made tremendous progress in the investment of the country in basic research and

in translational research, as evidenced by the development of the HPV vaccine and development of HPV testing, but we're in the transition period. And I was wondering if you could comment on projections of how HPV vaccine will affect HPV screening, particularly with your test, in the years to come.

DR. MAJEWSKI: So the specific question is about the impact of the vaccination rate on the performance of the test. So I would like to ask Dr. Wright to comment.

DR. WRIGHT: Tom Wright again.

Slide up, please. I think there's no question that once there's widespread vaccination in the United States, we will start seeing an impact on, first, HPV prevalence, especially 16 and 18. A lot of effort is going into surveillance in the United States to document this. Prevalence of cytologic abnormalities, they've dropped considerably in Australia and the areas where they've done good vaccination efforts, and the prevalence of high-grade disease.

The magnitude of this effect is going to depend on several things. The vaccination coverage. We currently have relatively low coverage in the United States today. The number of doses. Do they get all three doses? We relatively have few women getting all three doses. Only about a third, according to the CDC surveys, of all women, not of women who start the vaccination. And then the age of vaccination. The earlier you vaccinate,

the more the impact is on reduction of cervical disease. And we are tending to vaccinate most heavily in 16- and 17-year-olds, which in Australia has been shown to be less effective than vaccinating 13- and 14-year-olds.

So the reduction in CIN2 is going to reduce the positive predictive value of both cytology and HPV testing. I think most people, such as Eduardo Franco, who have evaluated this, they believe that since cytology is more subjective than HPV testing, that cytology will be impacted more than HPV testing.

Does that answer your question, Dr. Burk?

DR. BURK: I mean, I think it gets at the qualitative aspects of it. I was wondering, have you made any more analytical analyses?

DR. WRIGHT: We have not.

DR. BIRDSONG: George Birdsong.

I have several points I'm going to make. First, just to somewhat address your question -- it doesn't answer it directly -- about HPV-negative cancers. I think one of the largest studies also did come from Kaiser. It was published in *The Lancet* in July of 2011 and they -- okay, approximately what? Eighty cancers. They had a 31% HPV-negative rate. That was using a different technology but, I think, primarily hybrid capture.

The second point I wanted to make is, we saw data with this technology with eight cancers and then some other cancers from the New Mexico cancer registry, and the cobas detected -- or would have detected --

all except the non-cervical cancer, according to this data. But the numbers were so small it's hard to draw any conclusions either way from that.

And there have been several other studies that find, as was pointed out, varying HPV-negative rates. And one of the things I wanted to ask the Sponsor is, do you know if there were different cases missed by the cytology versus HPV, or did they tend to miss the same cases, which might suggest just a sampling issue?

And the reason I am focusing on the cancers is most of the analysis is kind of necessitated by the relative infrequency of invasive cancer. Most of the data is CIN3+, which is really mostly CIN3, probably 90-plus percent, give or take a little bit. And yet, in a cervical cancer screening program, the last thing you want to miss is a prevalent invasive cancer. And so I think it's important to bear that in mind as we are evaluating.

Obviously, the HPV seems to be significantly superior in detecting the pre-cancerous disease, and there's obviously value in that. However, I don't want to trade off detecting more pre-cancerous disease, which will presumably, long term, lower the population burden of cancer for missed prevalent cases, you know, for the lack of a Pap test that would occur in co-testing. And from the data we've been presented, I'm having a hard time analyzing that. But that's one of my concerns with this.

And then my final question was -- Dr. Wright correctly pointed out that there's considerable inter-observer variability in evaluation of

cytology and particularly around ASC-US. Less so for the more severe categories that he showed, invasive cancer or CIN3; the inter-observer variability tends to decrease. However, there's also inter-observer variability in the evaluation of the histologic specimens that are kind of used as a reference here.

So I'm just wondering, were there any -- you didn't say very much about how that was controlled for. So I'm assuming there were multiple pathologists on the consensus panel. But was anything else done, such as a p16 or anything that would allow you to kind of objectify the evaluation of the histologic specimens?

DR. MAJEWSKI: Christoph Majewski again.

So just to recap briefly, I heard you asking two questions. One was basically about any cancers that were missed by an HPV test, whether there was any cytology information on that, as well. That was the first part. And the second question was really about how was the histology adjudicated in the ATHENA trial. So I will ask Dr. Behrens to come up to answer that question.

DR. BEHRENS: Yes, slide up. Okay. This was a summation of the cancer study that we did, and we had 26 evaluable samples. And 25 out of the 26 were positive for HPV, and that included the one undifferentiated case. And the cytology, it was 23 out of 25 or 92% versus 96.2% for HPV.

We also did an additional study. This data hasn't been

reviewed by the FDA, but we did want to look at more cancer cases with our test. So we did a study at the University of Cape Town in South Africa, and we were able to obtain 50 additional samples from women who had been diagnosed with cancer and were presenting for treatment. And these samples were put in liquid-based cytology, the cobas test was run on that, and the pathology was adjudicated by Dr. Wright and Dr. Stoler. And next slide up, please.

What we saw in that study was, out of the 50 cases, 47 were positive for the cobas test. Of the three that were negative, one was positive for HPV 82, which isn't ordinarily considered an oncogenic HPV genotype. It isn't included in our assay. And the two others that were HPV negative were taken from visible large fungating lesions, which ordinarily we would not be depending on the HPV test for a diagnosis. They would be biopsied. And I have to think that those were probably sampling limitations.

So all in all, we had 26 and 50 -- we had 76 cases, and out of those only four were negative by HPV. Of the 26 cases, three were negative by cytology. We don't have cytology on the University of Cape Town samples.

DR. MAJEWSKI: So the second question was about the adjudication.

DR. BEHRENS: Sorry?

DR. MAJEWSKI: The adjudication problem.

DR. BEHRENS: The adjudication, okay. By protocol, we had an

adjudication of the pathology. And the way that worked was two cervical pathologists would first review the slides, and if there was agreement on histology, then that was the study diagnosis. If the two cytologists didn't agree, then it went to a third. And if two out of the three agreed, that was the study diagnosis. If none of the three agreed, then it went to a consensus reading where the three pathologists would sit around a three-headed microscope and come to a conclusion on that.

Does that answer the question?

(No audible response.)

DR. BEHRENS: Okay, thank you.

DR. CALIENDO: So we're going to have two more quick questions, Beth and Robbie, and then we'll have a break.

DR. UNGER: This is Beth Unger.

And I think your demographics -- you showed how it really represents the United States screening population, but it wasn't as representative of the women who actually get cervical cancer. And I wasn't clear, in your follow-up population, how your demographics followed along and if you were able to look at the performance in Hispanic minority groups as a separate group. I know you did a lot by age.

DR. MAJEWSKI: So there are two elements to your question for clarification. So the first element basically is what are the demographics in the follow-up? So just keep in mind that follow-up was performed on all

women who had basically a colposcopy at baseline, which means all of the HPV positives, all of the cytology positives, and the randomized patients.

And then the second part of the question is about the specific performance in the Hispanic population. So I would ask Dr. Behrens to come up to the stage and answer that question.

DR. BEHRENS: We don't have the demographics of the follow-up population on a slide, but we could prepare that and present it after the break. We also did do a post hoc analysis in different ethnic groups, and we do have the breakdown for just the Hispanic population. Yes, we'll get that up for you in a second.

DR. UNGER: And African American.

DR. BEHRENS: But I can tell you -- I'll just speak to it. The candidate showed the same superior performance in the Hispanic population as it did -- the numbers were almost exactly the same.

DR. UNGER: And African American?

DR. CALIENDO: Actually, it might be best -- we'll have a chance, when we go to the Panel, to show those data.

DR. BEHRENS: Okay.

DR. CALIENDO: Go ahead, Robbie.

DR. BURK: So I just have a quick question on your last data where you tested specimens that had cervical cancer. Although the real goal is to prevent cervical cancer, the detection of cervical cancer is obviously

important. How was this study done? Were you given just 50 cervical -- whatever it was -- cervical cancers, or were these blinded and also contained cervical cancer-negative or HPV-negative samples in that study?

DR. MAJEWSKI: For the specific Cape Town study, I can ask Dr. Behrens to provide you the details.

DR. BEHRENS: Catherine Behrens.

This wasn't a blinded study, and we didn't have any negative ones. This was specifically to see if our test could detect cancer because of the concerns about the physiology of cancers and deletions, et cetera. So this was just to obtain as many cervical cancer samples as we could and just see that the test was positive.

DR. CALIENDO: Thank you.

Okay, we're going take a break now. Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any member of the audience. We will resume promptly at 10:05.

Thanks.

(Off the record.)

(On the record.)

DR. CALIENDO: So please take your seats. We now will hear from a guest speaker, Dr. Garcia. Dr. Garcia, you may approach the podium and begin. You will have 40 minutes to speak.

Thank you.

DR. GARCIA: My name is Francisco Garcia. I'm the Director of the Pima County Health Department and also a distinguished professor of public health at the University of Arizona. I'm pleased to be able to attend the meeting today.

Could we get the slide up on the big screen? Thank you.

So Dr. Kate Simon asked me to give a little bit of historical context as to how the evolution of the cervical cancer screening guidelines has occurred, and specifically how HPV has been in consideration throughout their evolution. So that's my job today, and I do it from the perspective of population-based health.

My objectives are really twofold, to review our current understanding of epidemiology, natural history of HPV infection, and cervical cancer precursors, things that are really well established in our field and things that are not entirely -- almost entirely beyond dispute; but also to discuss the evolution of screening guidelines and how they apply in public health settings. I will not review or comment on the primary screening data that is being presented today by the applicant.

It's not that long ago, when I was in medical school, 1988, when people were still scratching their heads about whether herpes caused cervical cancer. And it seems a long period of time, but it actually wasn't that long ago, and to think about how the field has shifted tremendously in this particular arena really gives one pause.

We've learned that really cervical cancer and its high-grade cancer precursors really are kind of the tip of the iceberg to a variety -- a big reservoir of infection that either manifests itself as low-grade disease or warts or most commonly as asymptomatic infection that is transient, that will never turn into anything, and that will resolve spontaneously in the immune-competent individual.

This is a graphic that was shared by Dr. Mark Schiffman many, many years ago with me, and I use it because I think it encapsulates in many ways, I think, in a really concise way, what we know and what we don't know about cervical cancer screening.

If we start off by thinking that folks start off with a healthy reproductive tract, somewhere in the course of becoming sexually active, most of us, 88%, 85% of us, will encounter HPV infection sometime during the course of the onset of our sexual activity. In the vast majority of cases, that infection is resolved spontaneously. But when that infection is not resolved spontaneously, that is, when it persists, that really becomes the setup for what becomes pre-cancer.

However, even when there is that progression from persistent HPV infection to pre-cancer, to CIN3, even in some of those cases, perhaps as many 10% to 15%, there will be some spontaneous regression, and it's only those that don't spontaneously regress -- the vast majority of the CIN3's -- that if left unchecked, developed into cancer.

This process from a normal lower genital tract to an invasive lesion is luckily a multi-year process that probably takes at least a couple of decades so that we have ample opportunity upon which to intervene as a public health entity in order to prevent the development of cervical cancer.

This is a graphic that shows the point prevalence of high-risk and all HPV in a population in Manchester, England, but this really could be any population. This could be our border population down in Pima County. This could be a population of folks in almost any part of the world. The punch line here is that point prevalence of high-risk and all HPV types is really the highest when we begin to become sexually active. It's really the first few encounters, as we acquire our first few partners, that we will come into contact with this viral infection.

What's also notable from this graphic, and what has been consistent, is that there's actually a very sharp drop-off, and where that drop-off actually occurs, whether it's at 25 or at 30, the slope of that curve becomes quite steep at some point.

And even back then -- and this was in the late '90s and early 2000s -- we were talking about how we might incorporate HPV testing into a novel cancer screening paradigm. Wouldn't it be cool if we could use this very sensitive assay, if it was ever available -- wouldn't it be cool if we could use it to screen for cervical cancer? The challenge at the time was that we were screening indiscriminately. We were screening young women from a

very early onset, usually typically a few years after becoming sexually active, in some cases even before. And so that wouldn't have been terribly productive at the time.

This is from the New Mexico cancer registry, as Tom mentioned, the only population-based cancer registry in the U.S. And what it shows is a couple of things that I think are really important, that whether it's cancer or pre-cancer -- in this case CIS and adeno in situ -- the vast majority of infections that occur in women are going to be type 16 and 18 specific, and that among the women who have normal cytology, a very significant percentage of them -- in this case almost 30% of them -- will have an HPV 16 or 18 infection.

The question then becomes why do all of those infections not turn into invasive disease? And it is, thank goodness, due to the very healthy immune system that most young people and most individuals in this country enjoy.

When we think about specifically the role of 16 and 18 -- and 16 really being, from my perspective, probably the worst and most important actor -- we notice a couple of things, that 70% of all cases of squamous carcinoma are associated with those two types. But for adenocarcinoma, a type of neoplasm that's actually harder to screen for using cytology, that's actually harder to assess using that kind of a screening modality, it's actually 80-plus percent are associated with 16 or 18 infection. So that becomes the

rationale for the use of 16 and 18 in whatever screening paradigm.

Well, we've learned a lot, and we probably know more about this particular viral infection than we do about almost anything else. This is from Rachel Winer's study in Seattle, where she followed 500 young women from before becoming sexually active to the point that they became sexually active.

What she has demonstrated fairly conclusively is that it's not a question of whether an individual is going to become infected, but rather it's a matter of time after the onset of sexual activity, so that by the end of freshman year, by the end of the first 12 months, approximately 30% of the young women in this cohort were infected with high-risk HPV infection. By the end of their sophomore year, that had gone up to about 40%, and by the time they were graduating, it was almost 50%. This is a cumulative incidence, but it makes a point that this is a very ubiquitous infection that happens as people are becoming sexually active.

But just as rapidly as we become infected with this virus, our own immune system resolves these infections very efficiently, and in fact, probably more so in younger people as opposed to those of us in our 40s and 50s and older.

So this is a different study that actually looked at the converse. It followed a group of young women for a period of time after becoming infected, and really what they demonstrated is that regardless of the HPV

type, by the end of one year only 20% of the original cohort that had been infected was still infected. And by the end of two years, it was probably in the 10% range. And it is this group that really is the group that probably is at the greatest risk, and it is this group of young women that probably have a long lifetime ahead of them in terms of surveillance.

Tom reviewed some of the Kaiser Portland study data, but I think it's worth looking at again. What these investigators showed really beyond a shadow of a doubt is that despite the fact that high-risk HPV, as a group of 15 types that were included in the hybrid capture group, is a marker for elevated risk, not all high-risk HPVs are created equal, and that HPV 16 and HPV 18 are particularly bad actors, so that after becoming infected with one of these two, at the end of a follow-up of up to 10 years, you see very marked differences in the risk of developing CIN3, which is a true cancer precursor.

What's also interesting to me as a public health professional is the fact that for those young women who were high-risk positive but HPV 16/18 negative, although their 10-year risk was elevated, it was not tremendously more so than the HPV-negative group.

A different follow-up study from Denmark also looked at some of these same issues, and in this case the question was, what was the risk in young women who had a normal intraepithelial -- a normal Pap smear at the beginning of screening and observing them over a period of time? And what

you can see is, at 12 years follow-up, the risk for developing CIN3 for a young woman who has HPV 16 infection is almost 25% compared to women who are high-risk HPV negative, where it was less than 5%.

But as I said before, what really is most important is not these transient infections that are ubiquitous and that impact so many young people, but it's actually the persistence of this high-risk HPV infection. And the folks in Denmark were able to look at the issue of persistence specifically, and you can see that for folks who had persistence of their high-risk HPV infection, if it was a type 16 persistence, almost 50% of those young women developed CIN3.

So the interesting piece that we are challenged with in a public health setting is trying to figure out how we play with -- how we take advantage of our knowledge of the HPV prevalence and when it declines steeply, as well as how we connect that with what we know in terms of when CIN3, when the cancer precursor occurs, which is probably in the late 20s, and when cervical cancer incidence really peaks, which is in the early 40s. And we need to figure out where exactly to best deploy our screening technology, whether it be cytology or HPV or a combination thereof, or as yet some unknown technology.

Evelyn Whitlock did the evidence-based review for the Oregon Health Sciences Center as part of the U.S. Preventive Services Task Force review. And one of the things that she was able to demonstrate was

something that a lot of us had been observing for many years, and that was that really, above and beyond anything else, there was a very significant increase in the sensitivity of high-risk HPV testing compared to cytology. What is most important to me, though, as a public health entity is the consistency of the HPV results as compared to the variability that we see in the cytologic findings.

What has always been the great advantage of the Pap smear of cervical cytology has been its very high specificity. And regardless of what study you look at, I don't know of any studies where the specificity of a Pap smear has been less than the specificity of high-risk HPV testing. And it is in using that background and that rationale that really the concept of co-testing, or co-primary screening with both cytology and HPV testing, sort of came to be. And that's exactly how we got to this place. We knew that there was a greater sensitivity that was added by HPV, especially in that population of young women greater than 30 years of age. We also knew that a negative test was really a marker of a decreased risk in the long term.

We also started to identify some challenges, possibly the identification of small significant lesions, perhaps of CIN3, that were low-volume disease that perhaps could have regressed spontaneously. But certainly what we were able -- what was most important from a clinical standpoint was that adding these two technologies together really enhanced the predictive value, really enhanced what I was able to tell a young woman

sitting across the desk from me, what her risk was in the long term if she was negative for both.

So between 2009 and 2011, the American Cancer Society, ASCCP, and ASCP assembled a panel of experts to update and develop new screening recommendations that were based on a systematic evidence review. The process was overseen by a steering committee and was supported by a data group. There were six topical work groups, including one that actually looked at the role of primary HPV as a screening test, a group that I co-chaired. These groups drafted recommendations and rationale, which we posted for public comment, and this ultimately culminated in a consensus conference that finalized the recommendations in 2011.

The punch line is that we came up with some very strong statements of what should be done and what shouldn't be done and where HPV testing should be included and should not be included. But specifically we talked about the need to not screen anyone who was less than 21 years old. At that time it was kind of controversial how for 21- to 29-year-olds that screening could be lengthened to approximately every three years, regardless of what kind of cytology you were using, and actually made an affirmative recommendation against the use of annual cytology.

For the 30 to 65 age group, we talked about HPV/cyto co-testing as a combination that could be used if the desire was to go to increased screening intervals of up to five years -- and that was our preferred

recommendation -- or to continue with a cyto-only kind of screening as an acceptable kind of practice that was repeated every three years. But what was also very clear was that regardless of whether you were using cytology or HPV testing, that these screenings should not occur any more frequently than using these intervals.

So I began my career in this field in 1996, and in 2012 when we had this major alignment of all of these different entities in terms of the recommendation, to me, it was a major milestone. I had never actually seen that degree of agreement between all of the stakeholders at the table. And what came out that year, both from USPSTF, from ACOG, from the ACS-ASCCP-ASCP process, were relatively uniform, relatively consistent guidelines that, I think, make it a lot more likely for practitioners to follow because ultimately guidelines are only as good as the number of practitioners that we get to use them. So I thought that that was a pretty seismic event.

Back in 2011, our subgroup that reviewed the state of the evidence for primary high-risk HPV testing, we were tasked with seeing whether this was something that we could recommend at that time. What we found was relatively high-quality evidence that suggested superior sensitivity and negative predictive value of primary high-risk HPV testing. However, data assessing the specificity and the relative harms were very limited and of relatively low quality at that time.

Data was also limited to only women who were greater than 30

years of age and came mostly from Europe and from the developing world. And the thought was, were these populations sufficiently comparable to our own domestic population? And were these screening infrastructures -- in Europe, for instance, a very formal, organized screening process -- really something that could be imported into this country? We did think that it might be appropriate for settings with organized screening and referrals to specialized centers for evaluation, but we also knew that those conditions might not apply to all clinical settings.

In our brains were notable examples, and one that I had in my head was, well, I could see this working in a Kaiser, I could see this working in a very well run FQHC, but I don't see it working in the real world.

In sum, the primary HPV screening studies that we had to review at that time were mostly single-round, randomized controlled trials from Europe, again mostly demonstrating the higher sensitivity for CIN2 -- at that time it was CIN2+ -- as compared to cytology or HPV/cyto combo. We had a fairly good feeling that CIN2 probably was not the ideal endpoint and that CIN3 really was what we should be looking for.

There were actually only two studies that had more than -- that had two or more rounds, and what those studies at that time showed was that HPV detected CIN2 at an earlier stage. So the question was, were we doing anybody any favor? Was this real disease or was it not?

The other issue that came up at the time was, gosh, we can

figure out how to do HPV testing as a primary screen, but what do we do with the results? How do we triage the results? And this became a real sticking point for our work group. We could see a variety of different triage mechanisms, whether it's colposcopy, cytology, or some yet unspecified molecular biomarker or genotyping that would allow us to get to that point. But at least in 2011, we did not have consistent data on those issues that we felt were sufficient to really sort of take a stand.

With regards to genotyping as a potential triage study, as a potential triage strategy, really for all molecular markers there were very, very limited studies that were cross-sectional in nature, that were relatively small, that were largely archival, and no large-scale prospective studies with interval testing that we could depend on.

So even though we thought the evidence was terrific for the performance of primary screening, we thought there were far too many operationally unanswered questions for us to pull the trigger. But the language of the guidelines actually said that in most settings, this kind of primary screening approach is probably not appropriate in this country, leaving open the idea that there may be studies where that might apply.

Fast-forward to 2013, and we find ourselves with an embarrassment of riches with regards to data. And I'm not going to review all of these in any great detail but to say that it's a much different data landscape in terms of the follow-up that we had. For many of those very

same trials that we looked at back in 2011, now we have multi-year follow-up. And I'll just mention two.

The Rijkaart study, which is a Dutch observational cohort of 25,000 women between 29 and 61 years of age, that compared conventional cyto to HPV PCR. And what was really, I think, very notable and what has continued to reinforce my thinking in terms of this area is that clearly the CIN3 risk at three years for women who were 16/18 positive is so significantly higher than for women who are HPV negative, 26% versus .06%; and even compared to a cytologically negative woman, whose risk is approximately 2.4%.

The other, I think, really important trial for you guys to sort of wrap your heads around is the combination of data from the four randomized controlled trials of HPV and cytology. That includes data from Italy, Sweden, the UK, and the Netherlands, 176,000 women between 20 and 64 years of age with HPV testing done with either HC2 or PCR.

Really, what was very significant to me is that at three years, there was really not much of a difference between the two strategies. But it's after those first three years that we start to see some real differences. At six years after negative screen, the cancer cumulative detection rate was approximately 50 per 100,000 compared to less than 10 per 100,000 in the cyto versus HPV arms. And the detection of adenocarcinoma, which is such a difficult -- which can be such a difficult entity to detect, especially in its

precursor stages, was significantly better.

Tom showed you a much prettier graphic of the same data, but this is from their paper in *The Lancet*. But it clearly shows that up until three years, women who started with either a negative Pap or a negative cyto really had absolutely the same risk, but after that time you start seeing a real separation of these curves. That indicates a much higher risk for those women who were cyto negative.

I think there's still a lot of outstanding questions, and I think that we still need to wrestle with them. You know, primary HPV screening, in my brain, is clearly superior to cytology, but is it better than the combo of HPV/cyto? I'll tell you that, from my perspective, that question is still up for debate. I will tell you, as a payer and a provider of these kinds of services, strategies that mitigate our costs and our exposure, i.e., things that use a single objective test, from my standpoint, are more attractive from a public health standpoint.

Additionally, I also think that which triage strategy is most efficacious and cost effective still merits further investigation and follow-up, and ultimately what become the optimal screening intervals. And the Panel members brought that issue up.

Finally, how do we manage the HPV 16/18 negative but otherwise high-risk HPV-positive patient for the long run? We never thought that we would be in these management dilemmas. But I'll tell you that, in a

post co-testing world, we not uncommonly have a small minority of patients that have this persistent positivity that end up sort of coming back to us again and again and that we have to scratch our heads and admit to them that we're really not sure what to do.

So, in conclusion, from my perspective, cervical cancer prevention efforts have to balance safety and potential benefit. I think my bias as a participant in those processes is that our new guidelines are really based on improved understanding of our disease process and the limitations of screening, that we really are so much further ahead than we've ever been. And that's reflected by the degree of consensus across organizations.

Ultimately, as somebody who sits as both a policymaker and as a clinician, I realize that policy decisions are made from a societal perspective, but clinical choices that a woman and her clinician make reflect individual preferences and her perception of risk. This is one of those areas where we should think really hard about how to not do harm.

Thank you so much for your attention.

DR. CALIENDO: Thank you, Dr. Garcia.

Does anyone on the Panel have questions? Go ahead, Glen.

MR. FREIBERG: I have a point and one question. The first point is that although cost is important, it's not a consideration in the vote that comes later today. It was mentioned, so I feel obligated to mention that.

My question for you is in regard to your reference to cytology

as if it's the same everywhere. I am not as well educated as I should be on when a slide is read once, when it's read twice, when it's read by two different people. We saw from the Sponsor presentation earlier today that when you have a second read, there's a measurable discrepancy rate. So between all the European data you presented and the U.S., could you at least comment on how we should interpret what you presented from processing cytology samples?

DR. GARCIA: That's kind of a difficult question, and it's even made more challenging by sort of the realities of real-world clinical practice. In the setting of screening of large populations in this country, secondary adjudicated review is not a standard thing that occurs, and it ends up being something that is relatively rare. In the setting of these kinds of well-controlled, well-designed, population-based studies, there was in each case -- and I can't speak to it specifically, but in each case there were adjudicated review mechanisms that assured the highest level of quality control.

But you're absolutely right; cytology does not perform the same in everybody's hands. And, in fact, from my perspective, that's part of the reason why I have an affinity for high-risk HPV testing, because I think that that actually does.

DR. CALIENDO: Other questions? Go ahead.

DR. SARAIYA: Thank you, Francisco. A great presentation. I have a comment and a question. My first comment was just to set the record

straight that there are many population-based cancer registries. New Mexico is only the cervical cancer registry --

DR. GARCIA: Sorry, you're right.

DR. SARAIYA: -- coming from CDC. But the other thing I wanted to mention was that, because of the 100% coverage that the cancer registries have, we have the ability to look at rare cancers, which is what we consider cervical cancer nowadays in the cancer world. And we have noticed that the trend for cervical cancer has decreased 4% per year in the ages under 30 -- you know, 20 to 24 or 25 to 29 -- and decreased by 2% between 30 to 39. So now the average number of cancers in the 25 to 29 group is around 528, with a median age of diagnosis of 49.

So having said that, I'm trying to grapple with the issue of age 30 versus age 25. And my question to you is -- we know 15% to 20% of CIN regresses, and 40% of CIN2 regresses, and these studies that you mentioned, in Europe they all looked at -- some of them looked at younger women, and some of them looked at older women. But the conclusion that comes from these meta-analyses -- and these are organized screening programs -- was to start screening at a later age using HPV-based screening. Can you comment a little bit on that?

DR. GARCIA: It is one of those challenges, isn't it, because in this country we have a disorganized screening system, we have an opportunistic screening system, and in many ways that was -- kind of a lot of

the deliberation of our work group sort of was around the issues of how comparable was this data. We have been seeing this sort of secular shift in decrease in the number cervical cancer cases. We know that those cervical cancer cases are occurring more frequently in foreign-born populations, in immigrant populations, the kind of people that are served in our jurisdiction, in individuals whose screening history may be even more compromised or maybe harder to determine than the average U.S.-born individual.

So I wrestle with that 25 to 30 age issue too. And I can't tell you that I've come to a conclusion, but what I find compelling is the fact that such a high proportion of the CIN3's are in that 25 to 30 age group that it makes me want to intervene. But that's based on my impression and not on any systematic data review.

DR. SARAIYA: But what about the European trials that have looked at HPV primary screening and come to the conclusion to not screen until 30 or 35?

DR. GARCIA: It's that same challenge. I don't know, Mona, if the same sort of trend has been seen in Northern Europe. I'm not familiar with those data, and I'm not sure exactly how we would extrapolate that in order to come to some conclusion for that 25 to 30 age group. I really don't.

DR. PORTIS: I think what you said about how great it is that we have better screening tools is really important, though I think about what we've seen in other cancers, that sometimes more screening has led to over-

treatment, and I wonder if you have that concern here.

DR. GARCIA: You know, we absolutely -- I think those of us who sort of work in this area are very concerned about that. In fact, that's probably one of the main reasons that in fundamental biology, why we really sort of oppose screening anybody under 21, despite whatever anecdote people feel free to share. That will always be a concern. And so coming up with strategies that mitigate that become really important.

So the triage. The question becomes, is the triage that's being proposed going to be sufficiently -- will it sufficiently address that concern? In this case, not necessarily to generate treatment, unnecessary treatment, but to generate unnecessary procedures and unnecessary anxiety and unnecessary costs to the healthcare system.

DR. CALIENDO: So just for the record, that previous question was from Natalie Portis.

Go ahead.

DR. HILLARD: Paula Hillard.

You have very nicely summarized how there has come to be consensus in the guidelines and recommendations for screening currently, but I'm curious about your observations about how well those guidelines are being implemented by clinicians, their understanding of the guidelines as well as understanding of patients of those guidelines and the reasoning behind those guidelines.

DR. GARCIA: Mona probably has the deepest experience in this room in terms of what clinicians are doing and not doing. What we know from the ASC-US HPV triage experience was that it took some years for ASC-US HPV triage or high-risk HPV triage of ASC-US Pap smear to really sort of catch hold. And when it did, we consistently now have rates in excess of 80% to 90%, so much so that now we need to remind practitioners that if it's ASC-H, if it's ASC favor high grade, you don't need an HPV triage, so much so that we need to remind practitioners that, just in case you got a Pap smear on a 20-year-old, you shouldn't be doing HPV triage.

So you're absolutely right, guidelines are only as useful as they are implemented in a real-world clinical setting. That co-testing in our part of the world, in the Southwest, has a penetration of about 40%. That is very variable across different geographic regions of this country. And I think that there are educational pieces that need to be thought about. I also think that the complexity of what we've come up with, as good as it is -- and it's pretty darn good -- becomes a barrier at some point in terms of adherence to guidelines.

DR. CALIENDO: Angie Caliendo.

So my question is related. With the new guidelines out there, what percent of women do you think are being screened just by cytology?

DR. GARCIA: You know, I do not have solid information about that. What I can tell you is that in the state of Arizona, women in the public

sector, women who are cared for by county health departments and by family planning, Title X kinds of clinics, are three times, four times as likely to get screened with cyto only as opposed to cyto and HPV testing. Even though policy changes have happened at CDC and with Title X, that has been a little harder to have good penetration. I suspect that in our jurisdiction it would be about 40%.

DR. CALIENDO: So does anyone on the Panel have any insight into that?

DR. SARAIYA: Hi, this is Mona.

I do want to confirm that in the public sector program, with the federal health programs, we tend to follow the USPSTF guidelines. And just in 2012 is when HPV co-testing was approved according to the USPSTF, so we just implemented that. And even then it's really difficult for some of the programs to implement that.

In terms of national registries, there's really no way to look at what is happening, but there are surveys that we have conducted among providers and women, in terms of their acceptability. And the providers, those tend to vary by specialty and that the OB/GYNs are the first ones to agree with the newer guidelines.

It's the screening intervals that are the most problematic in terms of adherence, especially with the HPV and the Pap. There has been a tendency initially for the HPV and Pap to occur on an annual basis and now

there's an agreement to go every three years, but definitely not every five years for those women who are negative/negative. Older women are less likely to agree with the interval issue with HPV testing, but younger women seem to be more open to HPV testing and extending the screening interval.

DR. WAXMAN: Alan Waxman.

Just to underscore a comment that Dr. Garcia made, I also work in the Southwest. I work in a very poor state. I get questions from our state health department all the time about management in which HPV was not done. The reason HPV was not done is that the public clinics can't afford HPV and so they're doing Pap tests. A few of them, I think, are still doing conventional Paps, but most are doing liquid.

The other factor to keep in mind is we are now refining, very tightly, how we manage the screening of women who get screened. If we look at the women who get cancer, 50% of them never got screened in the first place. Another 10% of them got screened but didn't follow up appropriately. So whether they're getting screened every one year, three years, five years, with cytology, with HPV, with combination, it's getting that foot in the door in the first place that's really going to reduce the rates of cervical cancer.

DR. NOLLER: Ken Noller.

I don't have exact numbers, but as part of the certification process in OB/GYN, we collect data from one year of practice for all of the

individuals who are trying to become board certified. Based on review of those, I can tell you that most of the clinicians in this young age group, those that you might expect to follow the guidelines most closely, are still using cytology alone, though some in older women are using HPV plus cytology.

DR. CALIENDO: Thank you. Any other questions?

(No response.)

DR. CALIENDO: Thank you, Dr. Garcia.

DR. GARCIA: Thank you.

DR. CALIENDO: The FDA will now give their presentation.

I would like to remind the public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

FDA will have 90 minutes to present. Please begin.

DR. SIMON: Good morning. My name is Kate Simon. Dr. Kondratovich and I will be giving a joint presentation today to summarize FDA's review of the cobas HPV Test for primary cervical cancer screening.

The Sponsor has already familiarized you with the technical aspects of the cobas HPV Test, their clinical study design, and the flow of patients through their study. They have also described the demographics of the ATHENA study population and the distribution of cytology results and HPV prevalence in that population. They have introduced you to the candidate and comparator algorithms and have given you their summary of their

performance data. FDA believes the Sponsor's presentation of their data accurately reflects their study results.

In this first half of the FDA presentation, I will give you a brief history of the regulation of this device. I will also give you FDA's perspective on the published literature on HPV primary screening and what we believe are the unique aspects of the ATHENA study design and analysis. I will describe what FDA considers to be appropriate comparators for establishing safety and effectiveness of the proposed new indication. Finally, I will describe the influence of screening age on performance of the device for primary cervical cancer screening and the performance of the device in women subsequently diagnosed with cancer.

In the second half of FDA's presentation,
Dr. Marina Kondratovich will discuss the issue of women with unsatisfactory cytology results. She will also discuss the influence of a cytologist's knowledge of HPV status on performance, the benefit versus risk of the proposed new indication, and the limitations in evaluating future risk of disease.

The regulatory history of the device.

The cobas HPV Test is a qualitative in vitro diagnostic test for the detection of human papillomavirus in patient specimens. The test utilizes amplification of target DNA by PCR and nucleic acid hybridization for the detection of 14 high-risk HPV types in a single analysis. The test specifically

identifies the two highest-risk HPV types, 16 and 18, which are responsible for approximately 70% of all cervical cancers, while concurrently detecting the 12 other high-risk types listed on this slide.

The device is already approved for traditional HPV screening claims, one of which is for ASC-US triage. The indication for triage in women with ASC-US cytology to colposcopy based on HPV test results was originally approved in the 1990s. The cobas HPV Test has been approved for this indication since 2011.

The adjunct indication, which is essentially an indication for risk stratifying women 30 and older with NILM cytology-based on their HPV test results, was originally approved in 2003, and the cobas HPV Test has been approved for this indication since 2011.

You may notice that both of these indications make reference to professional guidelines and that detailed management guidelines are not specifically described in the indications. The main reason for this is that FDA does not dictate clinical practice. Clinical practice guidelines can be very complex and may make detailed recommendations that were not directly assessed in a sponsor's clinical study. Also clinical practice guidelines are subject to change, whereas approved indications tend to remain with a device throughout its lifetime, unless a sponsor decides to conduct a new study. Indications for HPV devices are therefore crafted to allow flexibility in clinical decision-making when appropriate.

The cobas HPV Test is approved for use with cervical specimens collected using endocervical brush/spatulas and placed in a ThinPrep Pap Test PreservCyt Solution. The study for the new indication utilized only this approved collection method for the cobas HPV Test.

The candidate algorithm put forth by the Sponsor is described by the proposed new indications for use for their device. It is important to note that this proposed new indication is not intended to replace the existing approved indications for use for traditional HPV screening claims. If approved, it would represent an additional indication for the test.

And since this slide is a bit wordy, this slide conveys the same proposed indication in a graphic format to help you visualize the proposed patient management scheme. The Sponsor has covered this, but since it is the core of what we are evaluating here today, I will remind you that per the new indication, the cobas HPV Test would be used as a first-line primary cervical cancer screening test.

Women who test negative for the high-risk HPV types by the cobas HPV Test should be followed up in accordance with a physician's assessment of screening and medical history, other risk factors, and professional guidelines. Women who test positive for HPV genotypes 16 and/or 18 by the cobas HPV Test would be referred to colposcopy. Women who test high-risk HPV positive and 16/18 negative by the cobas HPV Test, known as 12 other high-risk positive, would be evaluated by cervical cytology

to determine the need for referral to colposcopy.

Now I will cover FDA's perspective on the published literature on HPV primary screening.

Cervical cancer screening has been one of the most successful cancer screening programs in history, dramatically reducing the incidence of cervical cancer since it was implemented in the mid-1950s. Cervical cytology, commonly known as the Pap test, has always been the primary screening modality for cervical cancer. But the recognition of human papillomavirus infection as a necessary cause of virtually all cervical cancer has led to incorporation of HPV testing in the current cervical cancer screening paradigms.

HPV testing has long been considered a possible primary screening modality for cervical cancer, with many primary HPV cervical cancer screening studies conducted in recent years. I would like to emphasize that only the study conducted by Roche Molecular Systems in evaluation of the cobas HPV Test for primary cervical cancer screening is under evaluation today. However, FDA will briefly share our general perspective on the published literature regarding HPV primary screening in this introduction.

The vast majority of published HPV primary screen studies were conducted outside the United States where screening practices are different than in the U.S. Differences in screening practices, medical infrastructure, patient demographics, risk factors, and disease prevalence also do not allow

the results of such studies to be utilized to establish clinical performance characteristics in a U.S. population. Also the majority are randomized controlled trials with non-adjustable verification bias, which I will discuss in a moment. And, finally, the majority do not evaluate the role of 16/18 genotyping in HPV primary screening.

The majority of the study designs that look at HPV primary screening in the published literature are randomized controlled trials, or RCTs, in which the study population is separated into candidate and comparator study arms. In some cases this is an optimal study design, for instance, in a drug trial, when you can't give both a drug and a placebo to the same patient and expect to compare their performance in a single individual.

For IVD studies, you can usually perform multiple tests on a single patient, making randomization unnecessary in most cases. And in many ways, a randomized controlled study design is preferred for IVDs -- a non-randomized controlled study design is preferred for IVDs since there are fewer assumptions involved regarding the individuals tested by the candidate and comparator. You don't have to assume these individuals are fundamentally the same. You know they are the same. Non-randomized IVD studies also have double the statistical power of a randomized controlled trial of the same size. Also randomized controlled trials for IVDs may present unnecessary risks to study subjects if they involve managing patients per investigative test results and/or algorithms.

Ideally, disease is assessed the same for both the candidate and a comparator in a study. One way to accomplish this would be to do full disease assessment on all individuals in a study, but we all know this is often not possible, particularly if disease assessment involves risks to the patient.

Many of the randomized controlled trials that look at HPV primary screening in the published literature verify disease in different ways for different test outputs that may have different levels of risk associated with them. Depending on their test results and study arm, some women may undergo repeat cytology or HPV testing at a later interval, while others go straight to colposcopy. This creates a verification bias that cannot be overcome by statistical methods.

Verification bias occurs when a non-random group of subjects in a clinical study selectively undergo disease assessment. However, it is clear that sending all women in a cervical cancer screening study for disease assessment -- in this case, colposcopy -- is not a viable option if the goal is the least burdensome clinical study that minimizes patient risk.

One may try and minimize the verification bias in an HPV primary screening randomized controlled trial by sending all HPV positives in the candidate arm and all cytology positives in the comparator arm immediately to colposcopy. However, in this scenario, one is still sending twice as many women to colposcopy in the HPV arm as the cytology arm.

Keep in mind that if one sent the same proportion of women to

colposcopy in each arm, entirely at random, without any knowledge of any HPV test result, you would expect to see twice as much disease in the arm that had twice as many colposcopies, which should explain why the study design does not allow one to directly report and compare unbiased estimates of sensitivity and specificity.

I will describe how the ATHENA study is relatively unique in how it addresses this issue of verification bias for an HPV primary screening study, although one study published by Mayrand et al. has previously utilized a similar approach. Although every study design has its limitations, FDA believes that the ATHENA study was well designed to evaluate the proposed new indication for use.

The ATHENA study utilized verification bias adjustment to obtain unbiased estimates of sensitivity, specificity, positive and negative predictive values for the candidate and comparators. This slide illustrates the verification bias adjustment method used in the ATHENA study with a simplified hypothetical example of 10,000 women with low-risk test outputs.

Instead of assuming these women have no or insignificant disease, a subset of 500 of these women are sent for disease assessment and five cases of disease are found. In this scenario, would we conclude that we can expect five cases of disease per 10,000 women in this population of women with low-risk test outputs? Of course not. There are five cases of disease per 500 women, and therefore we can impute that there would be

100 cases of disease per 10,000 women.

In the ATHENA study, all patients had both the cobas HPV Test and cytology performed at baseline, and all combinations of test results shown here had disease verified the same way, with immediate colposcopy performed according to a standardized protocol and a centralized pathology review of all biopsies. I will refer to this disease verification procedure as being sent to colposcopy.

Not all patients were sent to colposcopy. All patients with either abnormal cytology or positive cobas HPV Test results went to colposcopy, and a small randomly selected subset of the lowest patients with high-risk HPV negative and normal cytology results were also sent to colposcopy. There were HPV tests that were not directly under evaluation that were also utilized in the study that could have a woman sent to colposcopy.

Disease status was imputed for the women who did not have colposcopy data from the women who did go to colposcopy based on their cytology and cobas HPV Test results and their age. With this study design it is possible to calculate the unbiased estimates of cytology and cobas HPV Test performance as sensitivity, specificity, and risk for cervical disease from these data for any combination of HPV/cytology test results for the entire study population without verification bias.

Here's that flowchart representing the proposed new indication

again, but the table below it allows you to quickly see which combination of test outputs sends women to colposcopy with the proposed testing scheme, depicted by the green squares.

Next, I will discuss appropriate comparators for establishing safety and effectiveness for HPV primary screening.

The clinical comparator for the evaluation of this new indication is cervical cytology alone. FDA believes this is an appropriate comparator in that it reflects longstanding clinical practice, is appropriate for all screening age groups, and is independent of any HPV test results.

The Sponsor is using the comparator algorithm as a benchmark for safety and effectiveness when evaluating their new indication, the candidate algorithm, which has been described. This benchmark is intended to represent clinically acceptable performance levels, not clinically optimal performance. Positive results are defined as women sent immediately to colposcopy, depicted in green by the table shown.

Positive results for the comparator are consistent with the 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests, which I will refer to as the 2006 guidelines. Per the 2006 guidelines, women with ASC-US or greater cytology can be sent immediately to colposcopy.

This comparator was selected prior to the 2012 update of the 2006 guidelines, which I will call the 2012 guidelines, in which immediate

colposcopy is no longer performed on women with ASC-US cytology and unknown HPV status. FDA still considers the 2006 cytology alone algorithm to be an appropriate comparator since it is more familiar to clinicians and has better sensitivity than the 2012 cytology alone algorithm.

The currently recommended cervical cancer screening paradigm involves HPV triage of ASC-US cytology results in women under 30 years of age and co-testing with HPV and cytology in women 30 and older. In this paradigm, women with cytology results greater than ASC-US, women who are ASC-US and HPV positive, or women with NILM cytology who are 30 and older and are positive for HPV 16 and/or 18 should go immediately to colposcopy. This algorithm is being included because it represents a higher bar for cervical cancer screening performance as a currently preferred algorithm, whereas cytology alone is considered acceptable.

In evaluating the proposed new indication against the acceptable and recommended cervical cancer screening algorithms, we are really comparing sending each of these combinations of positive test outputs to colposcopy. The primary difference between the candidate and comparator is that the candidate does not send women who are cytology positive and high-risk HPV negative to colposcopy but does send the HPV 16/18 positive women to colposcopy who are cytology negative or NILM.

The currently recommended cervical cancer screen algorithm differs from the comparator, in that it only sends HPV 16/18 positive women

with NILM cytology to colposcopy if they are 30 years or older, and women with greater than ASC-US cytology who are HPV negative do go to colposcopy.

The Sponsor has given you their summary of their test performance, and FDA again does believe the Sponsor's presentation of their data accurately reflects their study results.

The following slides will summarize the influence of screening age range on performance of the proposed new indication for use in detecting cervical disease. The slides in this presentation will show performance in detecting cervical intraepithelial neoplasia of Grade 3 or more, or ≥ CIN3, since it is less likely to regress than CIN2 and is generally considered a more robust endpoint. But please note, the general trends are consistent for the ≥ CIN2 endpoint which was in your Panel packets.

Values with significant differences in these slides will be shown in red. If we compare the performance of the candidate and comparator in detecting ≥ CIN3 in the entire proposed screening population, which is women 25 years and older, we see a statistically significant improvement across all performance metrics for the candidate. The candidate has better sensitivity and fewer false positives than the comparator and sends less women to colposcopy. The absolute risk of disease in women positive by the candidate is almost twice that of women positive by the comparator, and the risk of disease in women negative by the candidate is lower than for the

comparator.

If we compare the performance of the candidate and the currently recommended cervical cancer screening algorithm in the entire proposed screening population, we see a smaller but still statistically significant improvement in sensitivity, positive and negative predictive value for the candidate, which translates into higher absolute risk of disease for positives and lower risk for negatives. A similar number of false positives are seen by both methods, and both methods send a similar number of women to colposcopy.

Risk of disease for women positive by the candidate, shown in blue, is higher than for the comparator, shown in red. This improvement in positive predictive value diminishes but remained statistically significant -- remained statistically better in women 50 and older. The positive predictive value of the candidate is also higher than for the currently recommended cervical cancer screening algorithm, which is shown here in orange. And this difference is statistically significant in the younger screening populations, but not for women 50 and older.

Risk of disease for women negative by the candidate is lower than for the comparator. This improvement in negative predictive value seen with the candidate diminishes as women age, until this difference is statistically insignificant against the comparator in women 50 and older.

The additional comparator, which is the currently

recommended cervical cancer screening algorithm, is shown as the dashed line here due to the overlap. The negative predictive value for the candidate is better than this additional comparator for the proposed screening age range of 25 and older, is slightly worse in women 30 and older, and is not statistically significantly different in screening populations of women 40 and older or 50 and older.

An evaluation of the cobas HPV Test was conducted in cytology samples of women subsequently diagnosed with cancer. The Sponsor has covered this, but I'm going to give an additional analysis after this slide.

Eight cases of invasive cervical cancer were identified in the ATHENA clinical study, in which the diagnosis of cancer was made by a central pathology review, and the cobas HPV Test picked up all of these.

In addition to those cases, a series of bench pre-aliquoted, de-identified ThinPrep cervical samples from women who were subsequently diagnosed with invasive cervical cancer were obtained from an HPV/cytology registry at the University of New Mexico, independent of the ATHENA study. The diagnosis of invasive cervical cancer in the samples was confirmed by an independent expert pathology review panel. This slide shows the percent of these samples that tested high-risk HPV positive by the cobas HPV Test.

Please note that one sample was found to be an endometrial cancer and was not included in this analysis. That endometrial cancer was negative by both the cobas HPV Test and cytology. Another sample that was

invalid by the cobas HPV Test was also excluded from this analysis.

The women ranged in age from 27 to 84 years, with a mean age of 52 years. So, as the Sponsor showed you, it is true that 96.2% of these samples tested high-risk HPV positive by the cobas HPV Test.

But I just want to remind you all, although it's probably somewhat apparent, that this number does not reflect the sensitivity of the candidate algorithm in these samples, because a reminder that the positive results for the candidate algorithm are defined as women sent immediately to colposcopy. And per the candidate algorithm, women who are 12 other high-risk HPV positive with NILM cytology do not go immediately to colposcopy. There were two samples among the cytology samples from women diagnosed with cancer that fell into this category and therefore were subsequently counted as missed cases for both the candidate and the comparator, since neither algorithm would send these women immediately to colposcopy. Therefore, the sensitivity of the candidate for the combined cancer cases was 88.5% and the sensitivity of the comparator was 88.9%.

The candidate algorithm missed three cancers, two cases with results of 12 other high-risk HPV positive by the cobas HPV Test and cytology equal to NILM and one case that was high-risk HPV negative. And the comparator algorithm missed three cancers. These three cancers had cytology of NILM.

This concludes my portion of the talk. Dr. Marina Kondratovich

will now discuss a more detailed analysis of the data.

DR. KONDRATOVICH: Good morning. In the second half of FDA's presentation, I will discuss four issues. The first issue is related to additional analysis for unsatisfactory cytology results, why we need to consider this analysis.

The analysis, which was presented by Dr. Simon and by the Sponsor, does not include patients with UNSAT cytology because in this clinical study, patients with UNSAT cytology were not referred immediately to colposcopy. But the intended-use population for the HPV test, if this test is considered like primary screening indication, should include patients with UNSAT.

Consider, for example, patients with results of HPV negative. In order to obtain unbiased estimation, for example, a risk of disease among these patients, we need to include all patients regardless of their cytology results. So among these women, of course, it can be a patient with cytology results UNSAT. But in the analysis presented before, these women were not included because they don't have results of colposcopy.

The same for the patients with HPV 16/18 positive results. In order to obtain unbiased estimation, for example, risk of disease for these patients, we need to include all patients regardless of their cytology results. But in our previous analysis, it included only the patients with satisfactory cytology results. In order to address this issue, it performed additional

analysis, and I will present results of this analysis.

Second part is related to the influence of cytologists' knowledge of HPV status on performance.

In the ATHENA study, cytologists were intentionally blinded to all other patient test results, including HPV results, in order to avoid bias in the comparator, and here is comparator cytology test alone. So our comparator, which is cytology -- and if the cytology is abnormal, then we're considering that this test is positive for cytology algorithm. And if NILM, they're negative. And this performance is unbiased because it's really not -- does not have any influence from the HPV results. And it's the same like it's real-life setting.

Consider our candidate algorithm. In the candidate algorithm, all subjects with HPV negative should go to the follow-up, and for them, one don't need to perform cytology. The same for the HPV 16/18 positive results. These patients go immediately to colposcopy, so cytologies also don't need to be performed. So only for the subject with 12 other high-risk HPV-positive results cytology should be performed. So in real-life setting, cytologists know that essentially all specimens they're screening are 12 other high-risk HPV positive.

Can it be that this information can influence performance of our candidate algorithm? So in this ATHENA study, the performance of the candidate can be biased. So in order to address this issue, the Sponsor

conducted additional study with subset of slides from ATHENA study, and I will present results of this study.

The third issue is benefit/risk analysis, and the fourth spot is follow-up study, study design results and limitations.

So let us start with first issue, unsatisfactory analysis. In this study there were 0.43% of invalid cobas HPV results, and among these results there were around 27% of patients with unsatisfactory cytology. So you saw results for valid HPV results. So this was 99.57% of all patients, and among these patients, 1.8% have unsatisfactory results. So in order to obtain unbiased performance of the candidate or comparator, we need to consider valid HPV results which include unsatisfactory cytology. But analysis above does not include patients with UNSAT cytology results because, again, in this clinical study, patients with UNSAT cytology were not referred immediately to colposcopy.

In order to address this issue, additional analysis was performed. So this slide presents results for cytology and HPV results when unsatisfactory cytology results are included. So you can see that in this study there were 737 patients with unsatisfactory cytology, so all these patients with satisfactory cytology and these patients with unsatisfactory cytology.

Distribution of HPV results among the patients with satisfactory cytology is presented in this column: 2.9%, 7.6%, 89.5%. Distribution of HPV results among the patients with unsatisfactory cytology is presented in this

column: 2.6%, 7.1%, 90.3%. So this data does not contradict assumption that risks of CIN3 or greater for patients with unsatisfactory results are similar as for the patients with satisfactory cytology.

In addition, it was published paper in 2012, and one of the conclusions of this paper was that, for the ThinPrep cytology results, women with unsatisfactory results does not have higher risk than women with satisfactory cytology results.

Taking this in consideration, it was considering following analysis with model. It was considered that risk for patients with unsatisfactory cytology depends on HPV results and status and age. And this risk is the same as for the patient with satisfactory cytology results.

What does this mean? Like, for example, if we consider woman, a patient, with HPV 16 positive and this patient 29 years old and they have cytology unsatisfactory, in this model, we consider that this risk is the same as for the patient with HPV 16 positive, 20 years old of age and satisfactory cytology results.

So considering this model, we can obtain results for all patients, including this 1.8% of subjects with unsatisfactory cytology results. So this column presents basic performance characteristic of the candidate, which you already saw. This is without UNSAT. If we included UNSAT and model that the risk is the same as for the patient with satisfactory cytology, then you can see that the difference is relatively small, like this difference for

sensitivity/specificity. So performance of the candidate without UNSAT and with UNSAT is relatively similar. The same for the comparator. You can see that performance of the comparator without UNSAT is very similar to results with UNSAT.

In analysis which was presented, you saw comparison of this column to this column. This was results comparison without UNSAT. But if we included UNSAT cytology, then you need to compare this column to this column. And because these two columns similar and these columns similar, then of course all our conclusions about statistical significance in the performance comparison are the same.

Unsatisfactory analysis is especially important for the patient with high-risk HPV-negative results because among these patients there were 1.8% of patients with unsatisfactory results, and this woman is not going directly to colposcopy. In intended-use population, there are 89.6% of that kind of patient.

So the table in this slide presents results for risk of CIN or greater and CIN3 or greater for mainly this patient, high-risk HPV-negative subject. So according to our candidate algorithm, results for this candidate algorithm for this woman considered like negative.

So in this analysis, what you saw already, results without UNSAT. Risk, for example, for CIN2 or greater was 0.77%, and the risk for CIN3 was 0.27%. In the next column you can see results when we included

UNSAT, and in this model we considered like risk for UNSAT is the same like the risk for satisfactory. Then risk for CIN2 and greater is slightly larger, 0.78%. Risk for CIN3 is also slightly larger, but after rounding is the same, 0.27%.

We also can consider, for example, other model to check how sensitive this model is for our assumptions, that here in this column we consider that risk is the same. For example, let us consider that risk is not the same for UNSAT cytology but two times larger than risk for satisfactory, what kind of results we can obtain. If we can do this analysis, we see that, yes, risk for CIN2 or greater started to be even slightly more compared to 0.77; we can have 0.80. Risk for CIN3 or greater is also slightly greater, but after rounding it's the same, 0.27%.

So additional analysis showed that if patients with UNSAT cytology would have colposcopy results and were included in the analysis, the results which were presented will be similar to what you have already saw. UNSAT really does not have a lot of influence on the results, which already were presented.

Let me consider second issue, influence of knowledge of HPV status on cytology performance. As already I presented on similar slides, that for the candidate method, HPV negative does not need to have cytology. HPV 16/18 positive does not need to have cytology. So cytologists only perform for patients with 12 other high-risk HPV-positive results. So cytologists know

that essentially all specimens they screen really are 12 other high-risk HPV positive.

So performance of the candidate can be different in real life, not how we seen in ATHENA study. So in ATHENA study we see performance of comparator like unbiased performance, but performance of the candidate can be biased. So in order to evaluate this effect, the Sponsor conducted additional study with subset of slides from the ATHENA study.

The study design of this study was following:

Archived cytology slides from the baseline phase with histology, with corresponding histology diagnosis CIN2 or greater, were included in the study. Of course, in this study we have a lot of slides with histology diagnosis less than CIN2. So in order to avoid reading bias, of course, one can require to include all slides with histology results less than CIN2. But really we don't need to have that kind of big number of the slides with histology results less than CIN2. So around 1200 slides were randomly selected from a lot of the sets of the slides with histology results less than CIN2.

The cytologists at the original community laboratory where the initial reading was performed reread the slides. But in this study compared to the ATHENA, in ATHENA study, a cytologist was blinded to the HPV results, but in this study, cytologists were informed of the HPV status of the patient. It was like HPV 16 positive, HPV 18 positive, 12 other high-risk positive or

high-risk HPV negative.

So results of the study we called unblinded candidate, where in ATHENA it was called blinded performance, blinded candidate, because again, in ATHENA study, cytologists were blinded to HPV results. But in this additional study, what we call unblinded cytologists know HPV status of patient.

Please note that knowledge of HPV status really can influence only diagnosis of the patient with 12 other high-risk HPV-positive results.

So on this slide is presented results of the study for the slides of patients with 12 other high-risk HPV-positive results. So in this study there were 89 slides with histology results CIN3 or above, 72 slides with CIN2, and 815 slides with histology less than CIN2.

So this is results of the study. Consider slides with histology diagnosis CIN3 or above. If cytologist does not know HPV results, percent of abnormal, 41.6. But if cytologists know HPV results, percent of abnormal, 56.2.

So knowledge of HPV status increases percent of ASC-US for the slides with histology more than CIN3 by 1.35 times. This percent divided by this, so we see increased by 1.35 times. The same considered slides with histology results less than CIN3, also we see that there are increases in percent of ASC-US for these slides. For unblinded treating it was 29%, and for the blinded treating it was 22.4%. So we also see that there are increases in

the percent of ASC-US even for the slides which -- and this slide does not have CIN3. So we see that really there are influences of HPV knowledge on performance of the candidate.

Using this information, using exactly these two values from this additional study, we can recalculate what can dilute our candidate method using this information from this additional study.

Please note that in our candidate performance, we don't need to do any adjustment for HPV 16/18 positive. That's because cytology does not have any influence. Also we don't need to do any adjustment for high-risk HPV negative because cytology is not performed for this patient. So what we need to do, we need to do only adjustment for 12 other high-risk HPV-positive subjects.

So in ATHENA study, it was 720 subjects with ASC-US. Total number in this category was this. But using this information from this external additional study, we can calculate that in reality, probably in real life, it will be not 720, but 936 slides with ASC-US.

Then, using this information, we can recalculate crude estimates, and we can recalculate those with verification bias adjusted estimates, and then we are obtaining what kind of influence we have because of knowledge of HPV status on cytology performance. So what is the result of performance for blinded candidate and unblinded candidate?

So we see that there is this influence and with knowledge of 12

other high-risk HPV-positive results. Sensitivity here some increased, and this was increased by 5%. It was decreased in specificity, so it was increased in false positive rate approximately by 0.5%. Also it was increased in the number of positive results. Positive results here is colposcopy, and it was increased by 1.11 times. So approximately more than 11% more you can have colposcopy results in real-life candidate unblinded compared to what you see in ATHENA study. It was some minor decrease in the positive predictive value, and it was some minor improvement in the negative predictive value, because really we have improvement in sensitivity of 5%.

So this additional study addressed the issue of how the candidate algorithm will be performed in real life and how the HPV knowledge affecting performance of the candidate.

In the third part of my presentation, on these next few slides I present results of benefit and risk analysis for the primary screening for intended-use population. So you already saw this data, so it's the same data of the study, only presented in slightly different way. Instead of considering all subjects, all patients in the ATHENA study, we considered, for example, only 10,000 subjects or, for example, thousands, the kind of numbers that we can use for both, for candidate and for comparator.

In our comparison, of course, we would like to consider candidate unblinded how it will be performed in real life. And, again, comparator in ATHENA study is unbiased performance.

So using information from prevalence which were obtained in our analysis, we know that among 10,000 patients, there are 97 patients with CIN3 or above and 82 patients with CIN2. So these patients in both -- this table, one for candidate, 97, and another 82, this is CIN2. So this is the subject with some cervical disease, and this is the subject without cervical disease.

So using information about positive predictive value/negative predictive value or sensitivity/specificity, the same type of information, only presented a slightly different way, we can calculate this true positive, true negative, which we can consider like benefit, yes, and false positive and false negative, which we consider like something negative, like we call risk.

Please pay attention that in this presentation, if we're considering that candidate positive in reality is true outcome, this is 16/18 positive or 12 high-risk other positive and cytology abnormal. This is for candidate positive.

For comparator, what is the meaning of positive? It means that cytology is abnormal. And for the candidate negative, in reality this is true outcome. This is outcome 12 other high-risk HPV positive and cytology NILM or high-risk HPV negative. And for comparator negative it means that cytology alone and results are NILM.

The next slide presents the same information, what you saw in the previous slide, but in this slide also there are number of tests and

procedures. So in this column there are number of cytology tests, number of HPV tests, and number of colposcopy procedures.

So in this benefit/risk analysis, candidate unblinded detected more CIN3 or above disease, 61 versus 41. Also candidate detected more CIN2, 27 versus 22. Candidate has less number of colposcopies, 514 versus 639.

With regard to the same kind of negative impact which related to false negative and false positive, the candidate missed less number -- fewer number of CIN3 or above, 36 versus 56. Candidate missed fewer number of CIN2, 55 versus 60. And candidate has less -- fewer number of false positive. It means that these patients were sent to colposcopy, but they really don't have disease. So it was 426 versus 576.

Next slide presents the same type of the data, benefit/risk analysis, but instead of taking 10,000 patients, we're considering 100 colposcopy procedures. So it's the same type of the tables, but only instead of having the same number of patients in these two tables, we have the same number of colposcopies, 100 here and 100 here.

Please note that in this analysis we will have different number of patients which should be screened by this different method in order to obtain 100 colposcopy procedures. For example, for the candidate, it will be larger number of women screened, 1,947 patients, when for comparator, in order to have 100 colposcopy procedures, 1,565 patients screened. Because

we have different number of patients in these two tables, even the prevalences are the same. Of course, we have different number of disease subjects in these two groups.

So let us discuss in more details table for benefit/risk analysis for 100 colposcopy procedures. For candidate unblinded, candidate detected more CIN3 or above, 12 versus 7. Candidate unblinded detected more CIN2, 5 versus 3. Another positive impact, that candidate will screen more women, 1,947 patients versus 1,565 patients, so approximately will be screened 24% more patients with the candidate method. With regard to negative impact, which we call here like risk, they missed 18 patients, and candidate has less number of false positive, 83 versus 90.

In the next slides, I will present results of follow-up phase, study design results, and what kind of interpretation and limitation we have with this study. Let me remind study design of follow-up phase.

In this study, all patients at the baseline have colposcopy results, and if the patients have CIN2 or CIN3 or above, these patients were treated. And the patients who have colposcopy results, who have visit colposcopy and during this colposcopy their histology was less than CIN2, this patient went to follow-up phase and then they have Year 1 visit.

At Year 1 visit, study design was different. At Year 1, all patients have cytology Pap test, and if the Pap test was normal, then these patients were not sent to colposcopy. So for this patient at Year 1, disease

status was not verified. If the patient has abnormal cytology results, abnormal Pap, then this patient went to the colposcopy. If during colposcopy they have CIN2 or CIN3 or above, these patients were treated. And patients with Pap results normal or patients with histology results during the colposcopy < CIN2 without cervical disease, these patients -- which is here light green box -- these patients go to the Year 2.

At Year 2, it was same design like Year 1. All patients at Year 2 have Pap results, cytology. And if the patients have normal NILM Pap results, they will not proceed to colposcopy procedure. If the women have abnormal Pap results, then they go to the colposcopy, and if during the colposcopy they have CIN2 or CIN3 or above, they were treated. So women with normal Pap results and women with histology less than CIN2 proceeds to Year 3.

At Year 3, it was different design; it was designed different from Year 1 and Year 2. At Year 3, all women were invited to have colposcopy. So during this colposcopy we have outcome like CIN2, greater than CIN3 or less than CIN2. Using this data, risk of disease for each interval -- like Year 1, Year 2, Year 3 -- were calculated like number of patients with disease divided by number of screened patients.

Please pay attention that when we calculated risk of disease for interval like Year 1, patients with NILM cytology in this analysis, consider it like the patient without disease.

Using all this data, using data of the baseline and all of this

follow-up phase study, we can calculate how we call current and future risk for all different combinations of the HPV test results and cytology. So let us discuss in details what kind of current and future risk we have for the candidate algorithm for particular four outcomes of candidate algorithm.

Again, candidate algorithm has four different outcomes:

HPV 16/18 positive. This patient should go immediately to colposcopy; candidate algorithm called positive. In intended-use population, we have 2.9% of that patient.

Second outcome, 12 other high-risk HPV positive and cytology abnormal. This woman, according to the proposed new indication for use, should also go directly to colposcopy, so our candidate algorithm is positive. In intended-use population, there are 1.9% of that patient.

Third outcome is 12 other high-risk HPV positive and cytology NILM normal. According to the new proposed indication for use, these patients don't need to go immediately to colposcopy, so our candidate algorithm negative. In intended-use population, we have 5.7 of that kind of patient.

And fourth outcome is high-risk HPV-negative patient. For the candidate algorithm, this is negative results. These women are not recommended to go immediately to colposcopy, and in intended-use population we have 89.6% of that patient.

Using information about colposcopy at the baseline, we can

calculate probability of detecting cervical disease at the baseline, and in this presentation, this probability called like current risk. Current means that risk for cervical disease at the time of cytology and HPV testing.

Using the follow-up phase of the study, we can calculate what we call future risk. This is the probability that cervical disease will be diagnosed over the next three years of follow-up. And I would like to emphasize in the study with this design, so when we call future risk, this is the risk of cervical disease in future, with regard to the time of cytology and HPV testing.

So this slide presents basic results of current risk and some of the current and future risk at three years for all these four possible outcomes for the candidate algorithm.

So you can see like for HPV 16/18 positive is 15% at the baseline, so these two groups of patients are candidate positive. They go immediately to colposcopy according to new indication for use. Risk is 15%, 7.8% at the baseline. And then for these two groups of patients, candidate algorithm is negative. We don't send this woman immediately to colposcopy. Risk at the baseline, 2.8%, and for high-risk HPV negative, 0.27%. And this column presents risk, some of the current and future risk at three years, so 21.1%, 11.1%, 3.6%, and 0.34%. Let us discuss these four groups in more details.

Consider patients with HPV 16/18 positive results. In intended-

use population, 2.9% of this patient. According to the candidate algorithm, patients with this HPV result should proceed to colposcopy. The current risk calculated at the baseline for CIN3 or greater was 15.0%. If we try to use follow-up data in order to understand what kind of information about baseline risk bring for us follow-up study, then we can consider that -- if we consider that all CIN3 cases detected during three years were probably present at baseline, then the risk of CIN3 or above at baseline can be as high as 21.1%.

Consider second group of patients, patients with 12 other high-risk HPV-positive results and abnormal cytology. In population, there were 1.9% of that patient. According to the candidate algorithm, patients with this HPV and cytology result should proceed to colposcopy. And the current risk, baseline risk for this patient, for CIN3 or greater was 7.8%. If one considers that all CIN3 or above cases detected during three years after baseline were probably present at baseline, then the risk of CIN3 or above at baseline can be as high as 11.1%.

Consider third group of patients, patients with 12 other high-risk HPV-positive results and cytology NILM. In intended-use population there were 5.7% of that patient. According to the candidate algorithm, patients with this HPV and cytology result are not referred immediately to colposcopy, so our candidate algorithm is negative results. The current risk, baseline risk, of CIN3 or above for this patient was 2.8%. If one considers that

all CIN and above cases detected during three years were probably present at baseline, then the risk of CIN3 at baseline can be as high as 3.6% with upper limit of 95% confidence interval of 4.5%. So we're sure we're 95% confident that this risk at the baseline is not more than 4.5%.

For this patient consider real-life scenario. One would like to know the risk of CIN3 or above after one year for patients who were not referred immediately to colposcopy. And in this study we saw this value, current plus future risk at Year 1, 3.1%. Can I make some kind of relationship of this 3.1% to the risk in real-life scenario? In our study, when we calculated 3.1% like risk for CIN3 and above for Year 1 -- so baseline plus Year 1 -- then really we calculated risk only for this CIN3 and this CIN3. But in patients with CIN2 detected at the baseline, were treated. And in real-life scenario, patients are not referred immediately to colposcopy. So some subset of CIN2 could progress to CIN3 by Year 1. Also, at Year 1, patients with NILM cytology were not referred to colposcopy. And among them it can be some missed CIN3 or above.

So all of these two categories were not included in our calculation of risk, 3.1%. So we can conclude, that value of 3.1% probably is understated risk of CIN3 for that kind of woman who don't go immediately to colposcopy and then have visit on next year.

Consider patient with 12 other high-risk HPV-positive results and NILM. If one considers that, for example, half of CIN2 cases at baseline

will progress to CIN3 by Year 1 -- and at this risk to 3.1 -- so we obtained risk, 4.2. But still, this risk can be understated because we're really not considering patients who are missed by Pap test.

In order to address this issue, we can consider following logic, that by Year 3, all patients have colposcopy results. So all this missed CIN3, which were missed at Year 1 and Year 2, were included at the risk at Year 3. So this risk was 3.6%. But the value of 3.6% also can be understated because we're still not considering the risk to progress or progressing to CIN3 for the patients who were treated at the baseline because they had CIN2. So if we consider that half of this CIN2, for example, progress by Year 1, then this risk can be, for example, like 4.7 and this can be maybe more realistic.

Let's consider fourth group of patients with high-risk HPV-negative results, risk at the baseline. You saw this value already, 0.27%. If we consider that all CIN3 cases detected during three years were probably present at baseline, then the risk of CIN3 and above at baseline can be as high 0.34 with upper limit 0.66%.

But let us consider real-life scenario. One would like to know the risk of CIN3 and above up to three years for patients who are not immediately referred to colposcopy and are not screened for the three years.

In our study, we see that current plus future risk at Year 3 was 0.34%, how this value related to this real-life risk. In reality, it's related, but we can only tell that patients with CIN2 detected at baseline, at Year 1, and at

Year 2 were treated. So this risk was definitely not including this patient, because in real-life scenario this patient will be not referred to colposcopy at the baseline and also they don't have any screening for three years. So some of these women can progress to CIN3. So we can conclude, that value, what we see in this clinical study, 0.34%, probably is understated risk of CIN3 at Year 3 for evaluating real-life risk.

In order to address this issue, we can consider risk of CIN2 and above in this study, and we see that risk of CIN2 and above in this study is unbiased estimation because, at Year 3, all patients were referred to colposcopy. So all these subjects in the blue boxes, in reality, are here from risk about them, and this included at Year 3. So current and future risk at Year 3 of CIN2 was 0.94. And if we make assumptions that all CIN2 at the baseline, at Year 1 and at Year 2 progressed to CIN3 or above by Year 3, then it will be real-life risk; it will be almost like risk for CIN2 except this patient, 0.04%. So we can subtract 0.94 minus 0.4, and we obtain that real-life risk is greater than 0.34% and less than 0.90%.

This slide presents summary of what we already discussed for all of these four groups of patients.

The next slide presents additional information of risk of CIN3 for patients with various negative results. And you already saw this slide in the Sponsor presentation. This is the risk of CIN3 for the patients with NILM negative results. This is with HPV high-risk negative results. And if we

consider women with addition that it's not only high-risk HPV negative but also NILM negative, then we see some minor improvement in the risk.

In summary, issue with unsatisfactory cytology results was addressed by additional analysis. Issue with influence of HPV status on the candidate performance was addressed with additional study. Baseline-phase data with benefit/risk analysis presented by this table, we already discussed this table, and results of the baseline phase and follow-up phase for CIN3 or above presented by this table. And let me repeat again that this subject, positive, referred to colposcopy. This is their baseline risk, 15% and 7.8%. These subjects are not referred immediately to colposcopy; their baseline risk, 2.8%, 0.27%. And for real-life scenario, that these women don't go immediately to colposcopy, only on next year. Risk is more than 3.1. Probably maybe can be even like 4.7. And for this woman in this scenario, woman not going immediately to colposcopy and don't have any visit for three years, then real-life risk is between 0.34% and 0.90%.

This concludes FDA presentation. Thank you very much for your attention. Questions?

DR. CALIENDO: Thank you.

Are there any questions for either of the FDA speakers? Go ahead.

DR. NOLLER: Ken Noller.

We're going to be asked really two quite different questions.

(1) Is this proposed test appropriate for primary screening? And (2) should the age at which the screening is done be reduced to 25, as virtually all the guidelines currently in use in the United States suggest you don't use HPV testing primarily until age 30?

We have really not seen separate data, either from FDA or the Sponsor, on the 25- to 29-year-old age group. I would like to see that performance by one or both. The percentage of HPV positivity in that age group is about double the slightly older group. And I think we need to see that before we can answer at least part of one of the questions either now or this afternoon, particularly the predictive value positive and negative, the number of extra colposcopies, the rate of positivity.

DR. KONDRATOVICH: These slides present results for 25 and 29 separately.

So, Kate, would you like --

DR. SIMON: So this is just the 25- to 29-year-old age group. This is the CIN3 endpoint. You can see, in terms of how many women are referred to colposcopy, the candidate sends 10.58%, the comparator sends 9.8%. The additional comparator, which is the currently recommended cervical cancer screening algorithm, sends 7.21%. The positive predictive value for the candidate is still quite much better than the comparator, slightly better than the additional comparator. The false positive rate is lower for the candidate as compared to the comparator, and also significantly lower than

the additional comparator. Sensitivity is significantly higher than both comparators.

DR. KONDRATOVICH: With regard to colposcopy, this is a positive percent, all positive, because this is exactly patients who go to colposcopy. Candidate like 10.6% and comparator 9.8%.

DR. NOLLER: Right.

DR. KONDRATOVICH: So there it slightly increases the percent of colposcopy for the candidate compared to comparator for this particular age group.

DR. NOLLER: Thank you.

DR. KONDRATOVICH: And if you would like to see for CIN2, then next slides. The pattern of performance is the same.

DR. CALIENDO: Okay, thank you.

Other questions? Yes, go ahead.

DR. MASSAD: This is Stewart Massad.

Do you have any insights for us on how a random biopsy, which is not standard in the United States, might have biased disease ascertainment?

DR. SIMON: First, I'm just going to comment that the random biopsy only occurred in the case where there were no visible lesions. So it was not -- every woman did not receive a random biopsy. I do want to point that out. And I'm going to let Marina comment on that.

DR. KONDRATOVICH: Like this data right now is under our review, but we look at preliminary analysis, that conclusions about what is the relationship between performance characteristic of the candidate and comparator is approximately the same. Of course, this issue can be related to risk/benefit analysis, because in the risk/benefit analysis, when we consider it like this is true positive and we consider this benefit, it means that we not only detected disease -- the disease is present -- but it's also the disease is treated. It means that usually through usual colposcopy procedure, which will be done by community pathologist, it will be also detected and therefore this woman will be treated.

But this issue is really very difficult to evaluate because in this study, colposcopy procedure was intentionally blinded to HPV results in order to obtain unbiased performance. And in real life, when HPV -- for this primary HPV screening, HPV status will available. So community pathologist may use this information, so this issue definitely was not addressed in the study. But we can present performance, like directed colposcopy versus random biopsy.

DR. SIMON: And I'd actually like to turn that question back to the Panel, for those of you that are practicing OB/GYNs. Would you, if you saw any visible lesions -- because we have heard from some OB/GYNs within the FDA that it is not that uncommon to actually take a random biopsy if you don't see any lesions, and I'm wondering if the Panel would concur with that

or contest that.

DR. MASSAD: This is Stewart Massad.

Most clinicians where I practice would not take a random biopsy.

DR. WAXMAN: Alan Waxman.

The same.

DR. CAIN: Joanna Cain.

The same.

DR. NOLLER: Ken Noller.

The same.

DR. HILLARD: Paula Hillard.

The same.

DR. SIMON: Thank you.

DR. SARAIYA: Hi. Mona Saraiya.

I have a question. Can you tell me what the percentage of HPV, the positive for the 12 types and NILM, what the percentages were for -- you said 5.7%, but how that would break down by 25 to 29 versus 30 and older.

DR. KONDRATOVICH: This information is present in the Panel package, but we don't have, right now, that kind of slides exactly with breakage for these age categories. So my understanding, you would like to have this risk exactly separate for every age group. I'm correct?

DR. SARAIYA: Just from 25 to 29 versus 30 and older.

DR. KONDRATOVICH: For all patients or for only what kind of -- can you repeat again what kind of patient?

DR. SARAIYA: You know, in the algorithm, how many ended up being in the follow-up. You know, you have 5.7%. How many ended up having -- being high-risk positive for the 12 types, NILM, and negative for a 16/18, because they will be under surveillance. So I wanted to just know what the difference was between the younger population and the older.

DR. KONDRATOVICH: Yes. I'm not sure that we prepared, right now, that kind of slides, because we have slides when you have 25 and above all together or 30 plus together and this group is separately for this. But you would like to have 25 and then above. Yes, this is like --

DR. HOJVAT: Maybe we can get that information after lunch. Between the company and us, we can have that information.

DR. CALIENDO: Are there any other questions?

DR. SARAIYA: I just have one more clarifying -- two more clarifying questions on the comparators and the choice. I mean, I read their rationale and understand their rationale. But just to get it straight, it was cytology alone with the ASC-US triage as the main comparator, and the rationale for that was that that was accepted current practice, even though it might not be very common. And then the other practice was 30 and older, where you drew 16/18 triage. And, again, that is a relatively new practice. That's not necessarily -- you know, it's not even the preferred practice in

terms of doing 16/18 triage in those that are -- it's more HPV positive.

So I just wanted to understand that rationale for why you picked those two, because in reality I would say maybe there would be a variety where you'd have 25 to 29 and you would do the triage at the cytology. And then 30 and older, it just might be HPV, a generic pooled HPV test, not 16/18.

DR. SIMON: Well, the paradigm selected was -- it was selected as one of the currently recommended algorithms -- not necessarily -- there's no one absolute recommended algorithm, but as one of the currently recommended algorithms from 2012.

DR. KONDRATOVICH: And it was considered like additional comparator. The comparator is cytology alone, and additional comparator is this more complex algorithm.

DR. SIMON: Right. Because from a regulatory standpoint, the Sponsor needs to demonstrate that they have clinically acceptable performance, and if cytology is considered clinically acceptable, then that's the benchmark. And we put the other one up there in terms of what some of the more current -- you know, where cervical cancer screening has evolved to at this point. So we wanted to give both perspectives. That's why it's there.

DR. CALIENDO: Mona, does that clarify?

DR. SARAIYA: Yes.

DR. CALIENDO: Is there anything else? Go ahead, Al.

DR. WAXMAN: May I ask a question of the Sponsor or is that --

DR. CALIENDO: You will have time after lunch to do that.

DR. WAXMAN: Okay.

DR. CALIENDO: Yes.

DR. SIMON: Can I ask one more question, a follow-up question to Dr. Massad's question of the Sponsor, which is what -- you asked about a second round of screening. And from a regulatory perspective, we'd like to know what you hope to gain by doing a whole other round with this type of study design.

DR. MASSAD: Well, I don't know that you can do it with this kind of study design. This is Stewart Massad again. But the question is, if this is going to be assessed for safety and effectiveness, the big question about safety is, how often are you supposed to be screening people? Do we screen them daily? Do we screen them every month? It looks like it's okay every three years. Should it be every 5 years, every 10 years?

DR. SIMON: Right. So the question sounded more like a guidelines development question versus safety and effectiveness. Would you say that's fair?

DR. MASSAD: Well, I don't know that if the -- you can play games and say the intended use is left up to the clinicians. But, realistically, either this is a single-use test or it's a multi-use test. All the discussion that I've heard about it is that it will be employed as a multi-use test. So how

often should it be used? That's something that I think many of us are grappling with. We can decide that it's not relevant for the discussion today, but it's still up in the air.

DR. SIMON: Okay, thank you.

MR. FREIBERG: A partial response to that question is that there are already four indications for use in the package insert, and we're adding a fifth. So if you look at those other four, I believe they address your question.

DR. MASSAD: Actually, they do not.

DR. BURK: Robbie Burk.

I agree with Stewart exactly, that the goal is to protect cervical -- to prevent women for their lifetime from getting cervical cancer.

DR. SIMON: Right. The reason I asked the question was because I was thinking perhaps Dr. Massad was thinking of some studies, like the Kitchener study, where you're seeing different trends in subsequent rounds of screening. I would argue that possibly that may be due to the verification bias in those studies, at least to a certain degree. But perhaps not.

DR. BURK: So thinking more globally, across the wealth of studies or maybe the paucity of studies that have been done using screening using HPV alone, it looks like it's a very powerful test with strong negative predictive value, which should decrease the prevalence of disease at subsequent follow-up intervals out several years. And so while sensitivity and

specificity should stay the same, negative predictive value shouldn't be as good, and positive predictive value should be worse. But how much so, we don't really know from the data that we have, as far as I can tell.

DR. SIMON: Okay, I just wanted to understand the fundamental goal behind that question. So thank you.

DR. CALIENDO: Okay, anything else?

(No response.)

DR. CALIENDO: All right. So we're going to break for lunch, but let me just make a few comments. All the Open Public speakers that will be presenting this afternoon, please give your slides to LCDR Anderson so that we can have everything loaded. We have a lot of people who want to make public comments this afternoon.

Also there's a buffet for the Panel in the restaurant and a separate dining space for the Panel behind the bar. So we'll break for lunch. Panel members, please do not discuss the meeting topic during lunch amongst yourselves or any members of the audience. We will reconvene in this room exactly at 1:10. I will ask all Panel members to return on time. We have a lot to do this afternoon. Please take any personal belongings with you at this time. The room will be secured by FDA staff during the lunch break, and you will not be allowed back into the room until we reconvene.

Thank you.

(Whereupon, at 12:20 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:15 p.m.)

DR. CALIENDO: I'd like to resume this Panel meeting. We will now proceed to the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda. LCDR Anderson will now read the Open Public Hearing Disclosure Process Statement.

LCDR ANDERSON: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of the meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Thank you.

DR. CALIENDO: For the record, we have received multiple requests to speak for today's meeting. Therefore, I will go over the process to ensure a smooth transition from one speaker to the next.

You will have five minutes for your remarks, each speaker. When you begin to speak, the green light will appear. When the yellow light appears, you will have one minute left. When the red light appears, you will be done. If you do not stop talking, we will turn off your microphone.

(Laughter.)

DR. CALIENDO: We appreciate that every speaker remain very aware of their time so that everyone will have an opportunity to speak. We ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting. Okay.

LCDR ANDERSON: The first speaker is Dr. Warner Huh.

DR. HUH: Good afternoon. It's a privilege to address this Committee. I'm at the behest of the Society of Gynecologic Oncology as well as the American Society of Colposcopy and Cervical Pathology. My travel was covered by these two societies, and I don't have anything to report, except that I am a non-paid consultant to Roche. I sit on their publication steering committee.

Again, my name is Dr. Warner Huh. I am a practicing gynecologic oncologist at the University of Alabama at Birmingham, and I

have a specific clinical and research interest in cervical cancer prevention. I actually take care of numerous women that have invasive cervical cancer, and some of these women have been either unscreened or under-screened. But I think it's important for this group to recognize that many of these women had been regularly screened based on the current published guidelines.

I chair an interim guidance panel convened by the Society of Gynecologic Oncology, also known as SGO, as well as the American Society of Colposcopy and Cervical Pathology, also known as ASCCP, to develop clinical guidance on primary HPV for testing for cervical cancer screening. And I think it's important for this group to recognize that this panel was created in response to Roche's application for a claim for primary HPV screening. This panel included gynecologic oncologists, OB/GYNs, family medicine physicians, pathologists, epidemiologists, as well as experts in public health.

We recently had a face-to-face meeting on the 17th of February to create this clinical guidance document for providers who are considering using HPV testing for primary screening. And as a matter of full disclosure to this Panel, Roche presented the ATHENA trial data to this group via webinar and was also present at our face-to-face meeting. Roche's involvement was limited to addressing questions from the panel about data from the ATHENA trial. Full disclosures will be listed in the final clinical guidance document.

The target audience for this effort will be the community women's health provider. The final document is planned to present a

balanced discussion of pros, cons, and limitations on data on primary HPV screening, as well as guidance space and expert review of the literature supplemented by expert opinion on application of the test. While the panel has not completed its work, the panel's comments at this hearing are informed by the discussions of this diverse group of healthcare providers.

We do believe that primary HPV screening should be considered as another option or alternative to current U.S. cervical cancer screening paradigms. We are not suggesting that primary HPV screening replace current screening recommendations. In terms of comparative effectiveness, there are still a number of questions with regard to adoption, implementation, and acceptance, and we also need to compile data on the subsequent rounds of screening.

We wish to emphasize that no cervical cancer screening program will completely eliminate cervical cancer. However, primary HPV screening is as safe and as effective as cytology.

The ATHENA trial, in conjunction with evidence from European trials, provides highly compelling evidence that primary HPV testing has a higher sensitivity than cytology alone. And although not perfect, primary HPV testing misses less CIN3 and cancer than cytology alone. And based on the 2011 screening guidelines, cervical cancer screening -- as well as the United States Preventive Services Task Force screening guidelines -- cytology alone is a recommended cervical cancer screening strategy.

A substantial percentage of cervical cancer screening in the United States is still conducted with cytology alone, and if cytology is still recommended, it's difficult to see why a more sensitive test would not be. In regard to co-testing, the other recommended screening strategy, the risk/benefit ratio is not as clear.

It's also not yet clear when to initiate this type of screening, whether it be 25 years of age or 30 years of age. There's a substantial amount of CIN3+ in women between 25 and 29 years of age, and primary testing has the sensitivity to better detect this disease. However, use in this age group, in which HPV is common, must be carefully weighed due to the results in increasing the number of colposcopies and the possible risk of unnecessary treatment.

There is insufficient data to recommend a specific screening interval. It's presently three years with cytology and five years with co-testing. The ATHENA trial was restricted to three years of follow-up, and our group will likely recommend screening with HPV testing no sooner than every three years.

Additionally, controls for specimen adequacy and potential interfering substances need to be carefully addressed with primary HPV screening tests, as the morphologic examination from cytology will be lost.

Although there's a future possibility of simplifying cervical cancer screening with primary HPV testing, we have concerns about adding a

third option to the current recommendations and the error and confusion that this might create, as well as how women might transition in and out of different algorithms of cytology, co-testing, and now primary HPV screening. This highlights the need for implementation research and appropriate education of healthcare providers to minimize overuse and inappropriate use.

All in all, this group felt that primary HPV screening is a potentially very important scientific and clinical advancement of cervical cancer screening, since it holds the promise of improved or at least equal performance of cytology-based strategies. As with all new advances, there are many questions and concerns that are raised, and if primary HPV screening is approved, the group recognizes the immediate importance of providing sound clinical guidance as well as another opportunity to properly educate healthcare providers.

In the end, this panel is supportive of primary HPV testing. And thank you again for your time.

LCDR ANDERSON: Dr. Walter Kinney.

DR. KINNEY: My name is Walter Kinney, and I came from Northern California Kaiser to tell you what we are presently doing and why. I have no conflicts of interest with anyone. The vendors can't buy me a Coke. And the reason that's true is that I've been writing the internal guidelines for cervical cancer screening for Kaiser for the last 20 years. So I'm here as an individual. I don't speak for the organization, but I do speak with some

knowledge of the dataset.

I wanted to say two things to you. The first addresses Dr. Birdsong's earlier question about missed cancers associated with HPV testing. A few years back, we looked at the cancer antecedents in 6 to 42 months prior to the diagnosis of invasive cancer by histology, and we wanted to look starting at six months back because we weren't concerned about why people went to colposcopy and were diagnosed. We were interested in finding them prior to the development of their cancer and therefore thought that interval was relevant.

And in the adenocarcinomas, 18 of the 64 were co-test negative at 6 to 42 months, suggesting that there may in fact be the sampling issues that you mentioned. Both Pap and HPV were negative. Two were Pap positive and HPV negative. But 28, the largest group, were Pap negative/HPV positive. If, in fact, we want to make some headway against this group of cancers, HPV testing needs to be routinely included in screening. That was our conclusion.

The same thing, it turns out, is true for adenocarcinoma in situ. Far and away the biggest group was the group that were Pap negative/HPV positive in that same time period, 6 to 24 months prior to diagnosis.

The other thing that I wanted to talk about is that in June of 2012, we decided that the co-testing age limit should be taken down to 25, despite the fact that this was not nationally recommended and that doing so

comes out of our bottom line; we don't make more money doing this. We did that because there is cancer risk in 25 to 29 that looks much more like 30 to 34 than it looks like 21 to 24, because this is where there is a lot of CIN3. And you can't simply say we're going to detect that CIN3 later after the age of 30, because some of those folks do go on to get cancer. Because we thought that to make any progress against adenocarcinoma and adenosquamous carcinoma, we had to be including HPV testing.

And this is what happens if you do that. In 2003 and 2004, we were just getting this program going and we had it up and running by 2005 and the CIN3 went up more than twofold and stayed doubled. The AIS went up sixfold and stayed sixfold higher. The invasive cancers went up as we flushed out the prevalent disease and have come back down as we have continued to co-test people every three years. This is not entirely representative of the rates, because our population has gone up 20% in the time period that you see here, and those are numbers of cases, not rates. But we think this is not a home run; it's at least a ground rule double.

We think that simplification of the guidelines is essential, because if you're going to break the screening guidelines at 30 and the management of abnormals at 25, you end up with three age categories that the doctors need to know how to do different stuff for. And you try to teach the docs how to do this and it looks like this. That's one page out of eight of our algorithms from 2008. And you show this to the physicians, and they say

you're killing me here. I mean, there's not a chance that I'm going to remember this.

(Laughter.)

DR. KINNEY: And so we think that screening is going to stop under 25 in the vaccinated women. ASC-US triage store-and-sort was a huge headache. We're happy to see it go away. Co-testing permits enhanced quality control.

In the mid-2000s we rebuilt our cytology station so that we are showing our cytotechs the HPV result at their microscope, and all of the HPV-positive slides get QC'ed. It's not random the way it's recommended. And what do you know? In 2009 the facility that was doing this showed up with a lower cancer rate than the facilities that were not doing these things, and that has persisted through 2012. So we think there's some QC value. It makes the Pap smears work better basically.

And, finally, the HPV positivity in 25 to 29 is larger, but it's not unmanageable. The Pap-negative, HPV-positive rates in 30 to 34 are currently 6.1% for us, and those same rates in 25 to 29 are 10.1. So it's bigger, but it's not impossible.

And I'm out of time right there. Thank you very much. I appreciate your attention.

LCDR ANDERSON: Dr. Mark Schiffman.

DR. SCHIFFMAN: Hi, my name is Mark Schiffman. I am a

physician/epidemiologist at the National Cancer Institute. I've been working for 30 years on the etiology and prevention of cervical cancer. I'm speaking with the approval of NCI, but I'm not necessarily representing the official views of NCI. That's what I was told to say.

I'm here to present epidemiologic data we've recently generated in collaboration with Kaiser Permanente Northern California. You just heard Walter. And I want to give a specific data table that I'm motivated to bring here. The data strongly suggests that primary HPV testing conducted at three-year interval would be as safe as or safer than the two cervical screening approaches currently recommended, a three-year Pap or a five-year co-test.

Okay, here are my -- I need to advance. Here is the data source. Here are my collaborators. And here is my disclosure. NCI has received some epidemiologic research support from Roche and from BD at no cost for studies that we control.

So KPNC has the largest HPV testing clinical experience in the world, almost one million -- well, over now one million women screened. Routine co-testing is done at three-year intervals. The data are from 2003 to 2012. Enrollment is defined as the first screen in that interval, and we're restricted to ages 30 to 64. I'm presenting data from logistic regression and Weibull modeling, but we verified the five-year estimates using Kaplan-Meier simpler statistics and their robust estimates.

The laboratory methods at Kaiser Northern California is the conventional Pap, followed by the SurePath in 2009. And this is an important point, it's HC2 HPV testing. But I would like to say that this is directly relevant to your research today into the topic -- into your decision, I should say -- because hybrid capture 2 and cobas -- this is from the predictor study of Cuzick and Szarewski, but we also see it in 17,000 paired specimens that we've done in parallel of the two assays.

Hybrid capture 2 has around the same clinical sensitivity and clinical specificity as cobas. Cobas is analytically a little more sensitive, but not clinically much more sensitive. And so they are analogous. And I think it's an informative experience because Kaiser is so huge and you can really address the answer, a little bit, related to cancers. And you need a huge population to look at cancers, because cancer is a rare outcome in screening people.

Sorry, I'm not advancing. Could you advance? It's not advancing. I don't know what to -- ah, there. There's a little sensor.

Okay. So there's a large number of cumulative cases at KPNC. I regret those few seconds lost, but basically I'll get right to the point and skip a slide.

What I'm trying to show is that there are a lot of people -- there are one million people Pap negative, and we follow them; or HPV negative, ignoring Pap, we follow them. Or a negative for both. And you still see some

cancers: 173, 103, 72. But that's out of one million people followed for five years or more.

So I'm going to go right to the cancer slide, which is at the heart of what people are worried about and look at just the five-year risk, in the interest of time. Among Pap negative women, there is a very small risk of invasive cancer. Paps work; 0.031% over a five-year risk. HPV negative, though, is even safer, 0.017. And co-test is marginally even more sensitive. You can see that it is has a marginal increase in safety compared to the HPV-negative component.

If you look at the three-year, it shows exactly the same pattern. Pap is safe. HPV negative is even safer. And this is invasive cancers. Co-test is even slightly more, but very slightly more.

And so if you go back to CIN3, we have lots of power. I just wanted to flash that slide up and show that it has exactly the same characteristics.

So our conclusion, based on the biggest clinical experience we have, is that the risk following a negative HPV test is smaller than after a negative Pap, including cancer, and almost as small as after a negative co-test. And these data provide evidence, we believe, to support the relative safety of primary HPV alone at an appropriate interval, which we say conservatively would be three years.

That's it. Thank you.

LCDR ANDERSON: Ms. Dorothy Rosenthal.

DR. ROSENTHAL: Slides, please. I'm Dr. Dorothy Rosenthal from Johns Hopkins. I'm here as an individual, not representing any organization or any institution or laboratory. I've been involved in the practice of cytopathology for almost 45 years. I am a prior president of the American Society of Cytopathology, and president of the International Academy of Cytology. I've also worked as a medical director for a large clinical laboratory, doing over one million Paps back in the 1980s in California. I was the director of the cytology service at UCLA for 23 years, and now I'm at Johns Hopkins. I have stepped down as the director of cytopathology because I want the molecular era to proceed, and I am molecularly challenged, being of that age, and I've turned it over to our youngsters.

Let's see. I can advance this, I guess.

I'm here to discuss why I think it's important to proceed with HPV primary testing. I have been a proponent of the Pap forever. There we go, it's advancing. Thank you. There it is. Oh, okay, great. And yet I find that we still have some unmet clinical needs, one of which is accuracy; also reproducibility, simplicity, yes, and by all means patient safety. That's why we're here.

Well, no, that's a pointer. I may be hitting the wrong button. There we go.

When we talk about accuracy, you've seen bar graphs like this

before. This I downloaded from a webinar that was given by Dr. Tom Wright sometime in about 2009. It's from a group of publications across the countries that you see at the X-axis, and you can see that the sensitivity for the Pap is all over the board. The sensitivity for HPV screening -- can you proceed, please -- is much better and much more consistent. Thanks.

And so let's go on to the next one. If you put the two bar graphs together, you can see that there's a tremendous gain by using HPV testing to pick up our CIN2's and 3's. Next slide.

Now we get into reproducibility. This is from the recently published article which had our four laboratories from the ATHENA trial, and what I want to point out to you is Laboratory A. I don't know who that is, but they have a negative rate of 96.2%, which is way higher than it should be, which then inversely says that your rate of abnormals is very low. And within that negative 96.2% negative rate is a whole bunch of false negatives waiting to be detected, perhaps, in the next go-around of Paps.

And now we get to simplicity. I hope I can do this. Our triage strategy has been described so much and -- if you go to the next -- you can go online, Amazon.com, and for $10 download an app on your phone. I've done it. It's great. You have 12 choices. Next slide, please.

You put in your patient's age, her HPV status, if she's pregnant or not, and what her initial testing with cytology is. And then you can say to your patient, ah, now we know what we're going to do with you. Next.

And there's the same application as part of this little package for the histology management guidelines. Next.

And you can just keep scrolling through all of these algorithms, and no wonder that poor orangutan was flat out. Next. Next.

Okay. And so finally we get to patient safety. Next slide, please. And this is why we're here. And if we're not here for this reason, we should all go home right now.

The proponents of the Pap -- and I consider myself one. I've worked with it for over 45 years. If it ain't broke, don't fix it. But it still needs some fixing. We may have taken our Pap as far as we can the way we know it today. The success of the Pap has been because of the slow growth of most cervical cancers and the frequent screening intervals. And now that we're increasing our screening intervals, these women who are beleaguered -- and believe me, they are -- are not going to be dealing with their silent precursor lesion in time to get in for their next round of testing.

We see a plateau death rate, but I think in our arena it may be rising, anecdotally. And I've heard this from others. Also there are so many Paps that our cytotechnologists are really being pushed a bit too hard to get through them all. So next.

I'm asking the question, has our Pap, as we know it, outlived its time? Next, please.

I just want to say I am in full favor of HPV primary testing and

urge you to --

LCDR ANDERSON: Ms. Jennifer Smith.

DR. SMITH: Thank you to the Panel for letting us give a presentation today. I wanted to mention that I have received understood educational gifts or research grants from Hologic, Gen-Probe, Qiagen, and TrovaGene, and I've been a conference speaker for BD Diagnostics and Hologic and Gen-Probe. I have no funding, besides myself personally, for coming to this meeting.

The theme of this morning, in this morning's session, about why women get cervical cancer, I just wanted to remind us that it's true that we really need to make more efforts. And our efforts have been really trying to get women who have been under-screened or irregularly screening into screening; that 54% of the women who are getting cervical cancer haven't been screened. But we have to remember also the 29% of women who are getting screened, who have screening errors and are getting cervical cancer nonetheless. And I think that's the real opportunity of the co-testing as well as primary screening discussed here. And again, the remaining 12% not completing treatment.

The option of primary screening, I think, will allow programs with restrained funding to increase the number of women screened, while maintaining near equivalent sensitivity for the detection of high-grade cervical disease as compared to co-testing. And as you well know, programs

like the National Breast and Cervical Cancer Early Detection Program have funding restrictions.

In some states, including my own -- from North Carolina -- when the money from the program runs out of funding, it often can be in the middle of the year. Women who are under-screened or under-served are actually turned away from services. And this is a big issue in many states. It doesn't happen in all states, but I think that just shows how the constraints of funding exist within programs in our country. And with these limited budgets, I think that there are difficult programmatic decisions to be made between the cost per screening per patient and the number of total women better able to be screened.

This is actually a slide that came before the implementation of Affordable Care, looking at screening needs of under-served women from the National Breast and Cervical Cancer Screening and Early Detection Program from 2004 to 2006, published by the collaboration with CDC.

And just to highlight, on the top of the slide is the number of women estimated, at that time, who were age 18 to 64. These are, again, slides based on the previous guidelines of screening at the age of 18. But if you just want, I think, to look at just the bottom line, which is that of those women, roughly 8.8 million were eligible for the screening program, meaning that these are women who are 250% under the poverty line or less and fulfill economic requirements as well as other eligibility requirements. And of

those, only 8.7% of those eligible women were actually screened by this program. And so it just shows the big need that we remain to have.

And I think I would argue, also, that even with the implementation of Affordable Care Act, there will be many women who remain uninsured and who will actually need services beyond those that have insurance.

So in terms of the NBCCEDP, co-testing, as Mona mentioned earlier, is reimbursed within the program based on the U.S. Preventive Services Task Force recommendations. But the use of co-testing varies within the program, largely based on differences in provider and program preferences.

And I think it's important when we think, you know, as primary screening being another option on the table for physicians, what are the current co-testing rates in the United States? This is actually based on a random sample of ACOG members who were given a survey, and this is data based on 2011-2012. The questionnaire was sent to 1,000 of the ACOG members, and the response rate was 36%, which is often characteristic of medical surveys among providers, because basically the bottom line is that in this self-reported data of physicians, about 11% offer co-testing to women of all ages, 45% offer co-testing to women 30 years of age and older, and 21% offer co-testing only if the patient requested it, and 23 did not use co-testing at all, did not use HPV for screening at all. And co-testing was more

commonly used in the Northeast, least common in the South, and most common among university-based OB/GYNs.

So as you consider our provider-patient acceptability, obviously having one result may be less complicated to patients than having two.

Cost-effectiveness analysis. I was surprised, in the literature, how little data is available on comparing primary versus co-testing scenario, looking at potential three- to five-year intervals for implementation, as well as the potential inclusion of 20- to 25-year-olds -- 25- to 29-year-olds -- excuse me. Program changes obviously are going to occur with the decrease in the number of cytologies being conducted in primary screening scenario, and safety issues and a potential three-year interval as compared to a five-year interval.

So we believe that there is a need -- I'm speaking on behalf of the Cervical Cancer-Free Coalition -- in the United States for primary HPV testing as an option for both private and federally funded programs, such as the NBCCEDP, in addition to co-testing. And then also a big call. There is roughly one billion women estimated to not have been screened --

LCDR ANDERSON: Ms. Heather Banks.

MS. BANKS: Hello, my name is Heather Banks, and I do really appreciate the opportunity to be here this afternoon. I'm here today as a cervical cancer survivor. And I did receive compensation for my travel related to today's meeting from Roche Molecular Systems.

Six and a half years ago, at age 31, I had my first abnormal Pap, followed by a positive high-risk HPV test. At that time I was pregnant with my second child, and not even a year later, I was diagnosed with cervical cancer, now 32 years old with a three-year-old daughter and a three-month-old son.

One thing that sticks with me the most from the day that I was diagnosed is the pure shock and disbelief in my doctor's voice, that I had cervical cancer. If this can happen to you, it can happen to anybody, she said many, many times. And she still says it today when I do see her. You see, I wasn't a poster child for HPV or cervical cancer. I had always been on top of my health, receiving annual Paps and exams for 13 consecutive years. And I was always told that everything was fine. I was in good health, normal weight, non-smoker, and the sexual history of both myself and my husband was just about as innocent as it gets. Then suddenly, just 20 months later after my first normal -- my last normal Pap, I had cervical cancer. This wasn't supposed to happen to me, but it did.

I recently reached my five-year cancer survivor milestone, and while a lot of my cancer story is in the past, my life has been changed in many ways because of it, and I can't help but wonder how my life would be different if HPV and cervical cancer weren't a part of my story and my history. I often think about how different my life would be today if I would have been screened earlier for HPV using the best tests possible. Maybe I wouldn't have had to have a radical hysterectomy, chemotherapy, and radiation at age 32. I

probably wouldn't have had to go through menopause more than 20 years before I was supposed to. Maybe it could have prevented my now permanent condition called lymphedema, which has hospitalized me four times in the last five years. Or maybe I wouldn't have to wear compression hose and compression shorts on a daily basis and receive biweekly therapy due to my compromised lymph system as a result of my hysterectomy.

But in addition to all of this, maybe, just maybe, I wouldn't have to live with the fear in the back of my head, the one that never goes away, the fear of dying as a young mother. There's nothing more terrifying to me than the thought of dying as a young mom and a young wife. And while my health is good now -- and I have no reason to think otherwise -- cancer has instilled this lifelong fear of reoccurrence.

So today I ask you to think what if? What if today's decision helps my now eight-year-old daughter and all young women to have the opportunity to be screened early using the best tests possible when they are older? I can tell you that this mom would be really happy because it would just be one more way that I can prevent her from having to go through what I did. If the decision made here today can help prevent -- can help eradicate even one preventable cancer, think of how that would be life changing for women like me who wonder what if?

Thank you.

LCDR ANDERSON: Lee Shulman.

DR. SHULMAN: Good afternoon. My name is Lee Shulman, and I'm here today as a practicing OB/GYN and geneticist and representing no organization. I'm the Anna Ross Lapham Professor in the Department of OB/GYN at the Feinberg School of Medicine at Northwestern University.

For the sake of proper disclosure, I have been and continue to be a consultant for several healthcare companies, including those that are pertinent for today's discussion, Roche and Qiagen. However, I am here today at no one's invitation and completely at my own expense, having canceled the busiest clinical day of my week. That clinical week involves the application of cervical surveillance to women in their early 20s through the menopausal transition, as well as the training of residents and students.

During my previous 10 years at the University of Tennessee, Memphis, and the University of Illinois in Chicago, I directed the colposcopy services at those institutions. As such, cervical surveillance has been and continues to be a seminal part of my clinical teaching and research aspects of my career.

I had the good fortune to attend Cornell University Medical College, where we were all immersed in the work of George Papanicolaou. His accomplishments were presented in an almost reverential manner, and there is no question that his discovery and implementation of the Pap smear changed and markedly improved women's health. But this Panel is now considering further changes to cervical surveillance with what we have

learned in the decades since the incorporation of the Pap smear into women's healthcare.

I will not repeat the scientific and clinical information presented here today, but it has long been known that there are considerable and profound limitations of cytology to identify those women who are likely to progress to advanced cervical disease, and even to detect those cellular changes associated with that progression.

In the studies that showed the benefit of HPV co-testing, they highlighted the limitations of cervical cytology, and it was increasingly apparent that HPV would potentially provide a superior approach to community-based screening. And now the most recent studies presented by Dr. Wright and others here this morning actually confirm this, that primary HPV screening provides a superior approach to identify those women most likely to progress to advanced cervical disease.

Indeed, the protocols presented here today improve cervical surveillance while maintaining the benefits of earlier screening algorithms. Previous changes to the screening algorithms have not altered women's access to and utilization of their healthcare providers, a fear of many OB/GYNs around the country. George Papanicolaou did not know about HPV and thus developed a revolutionary screening protocol that allowed for the early detection of cervical cancer, so that surgical interventions would result in improved clinical outcomes.

The Pap smear is no longer geared to detecting early stages of cervical cancer. Rather, cervical surveillance is meant to identify premalignant cervical changes so that interventions can prevent the development of cervical cancer.

The failure to recognize the well-documented limitations of cervical cytology, in this regard, can only be explained by a choice to ignore the obvious or by motivated self-interests. It cannot be explained by a desire to provide optimal healthcare for women.

When the automobile was first introduced, there were many people who claimed that it would lead to calamity and societal breakdown. Many of those voices were from industries tied to equine-based travel, such as buggy whip manufacturers. There was nothing wrong with the horse, but the automobile represented a true transportation advancement that allowed our society to develop and achieve success that would have been impossible with animal-based transportation.

There's nothing wrong with cervical cytology either. But study after study has affirmed the superior ability of HPV to assess risk for progression to advanced cervical disease, as well as the detection of those women with cervical pathological changes that require intervention. Cytology remains a part of the primary screening algorithm, but its ability to provide optimal screening is no longer a question but an accepted fact.

I hope that you will agree that primary HPV screening is a more

objective and effective approach to cervical surveillance that will improve the health of women.

Thank you.

LCDR ANDERSON: Dr. R. Marshall Austin.

DR. AUSTIN: Good afternoon. I'm Dr. Austin from the University of Pittsburgh, and I have no financial disclosures. I'm really here today to speak on behalf of co-testing as providing the maximum protection for women in screening.

And with that in mind, I would point out that trials, such as what we've heard about today, that focus on a CIN2/3 endpoint cannot document protection against cervical cancer.

A number of questions remain that are focused on cancer. For example, one of the most difficult things that the Panel and the FDA will have to deal with, if this approval is made, is regulation of laboratory-developed tests, which so far have eluded the FDA. This was a case we saw, an advanced stage endocervical cancer five years after the woman had a false negative HPV laboratory developed test. HPV 16 was in the tumor, and she died.

Another case, an example from Magee-Women's Hospital. This is a woman who had a malignant ThinPrep cytology, biopsy confirmed cancer. She had a negative hybrid capture 2 HPV test from the ThinPrep vial.

In our own publication, there are about 10%, 3 of 31 women at

Magee, that have squamous carcinoma, test hybrid capture 2 negative, and they all had 16 or 18 in their tumors. The College of American Pathologists has similar data that's in press. I believe Dr. Birdsong is one of the authors on that paper. And these are the four largest international collections of cervical cancer cases tested with an FDA-approved HPV test, hybrid capture 2. And in these studies, 10% tested hybrid capture 2 negative. And that predictors study below that Dr. Schiffman mentioned, along with other data, shows that the Roche cobas test is not more sensitive than hybrid capture 2.

Furthermore, when you look back in time before the women are diagnosed with cancer, the false negative rate goes up for HPV. In the Kaiser data, 31% of the women diagnosed within five years after baseline testing had negative HPV tests. And if you look at the European trial data that was recently published in *The Lancet*, 8 of 19 or 42% of women diagnosed with cancer 2.5 to 7 years out had negative HPV tests.

Another issue that we haven't heard about in the discussion today that I think is important is the observation that was published by the pathologists from the ATHENA trial themselves, that when they did a subset analysis on the HPV-negative CIN2/3 cases, that using the Roche marker p16, that they had misclassified over 60% of those CIN2/3 biopsies, which I think calls into question the reliability of the CIN2/3 diagnoses in the entire trial.

Verification bias has been mentioned, but what people have not focused on is the low verification bias-suggested sensitivity in that trial

for both HPV at 61.7% and the Pap at 35.9%. And I think actually that may be related to over-calling CIN2/3.

The Kaiser data has shown that the best protection -- and I was glad we heard from a cervical cancer survivor -- the best protection against cervical cancer is with co-testing.

This is data from Magee showing Kaplan-Meier plots for cervical cancer risk. The Pap-positive/HPV-negative curve is low, but it's definitely higher than double negative. And when you -- can you give me the next slide, please? When you go out and look at the subset of women with prior abnormal Paps, what you actually see is the Pap-positive HPV cervical cancer risk curve is actually higher than the Pap-negative/HPV-positive curve after two years.

So, finally, I think the questions that remain for the Panel are, will the FDA be finally allowed to regulate HPV/LVT, which is now about a third of all HPV tests in the U.S.? What are we to make of the misclassification published in this one subset of the CIN2/3 cases? Is 61.7% really high enough for verification bias adjusted --

LCDR ANDERSON: Dr. Anna Mazzucco.

DR. MAZZUCCO: Hi, my name is Dr. Anna Mazzucco, and thank you so much for the opportunity to speak today. I speak on behalf of the Cancer Prevention and Treatment Fund, and I have no financial conflicts of interest.

After completing my Ph.D. in cell biology at Harvard Medical School, I conducted research at the National Cancer Institute, and those are the perspectives I bring today.

The question today is whether HPV testing should be the first-line screening tool for cervical cancer. We are concerned that this is a significant departure from current recommendations of the CDC and the U.S. Preventive Services Task Force as well as ACOG, ACS, and AAFP. Currently, HPV tests are only recommended in the context of co-testing with a Pap smear and only for patients 30 and older.

In this study, the comparator arm triaged all abnormal cytology ASC-US or higher with immediate colposcopy. That does not really reflect current clinical practice. Six percent of all women in the trial had abnormal cytology at baseline, so this clinical trial design actually resulted in a high colposcopy rate in the comparator arms. We also have other concerns as well.

The majority of cervical cancers occur in women who have never been screened or who were not screened in the last five years. What is most needed is to increase patient compliance with screening. We do not have evidence that the HPV testing would actually increase patient compliance. On the contrary, the proposed plan, based on the trial population, would result in 7% of women ages 25 to 29 undergoing immediate colposcopy, which is more expensive and more unpleasant than a

Pap smear. And we are concerned that this is likely to reduce the chances of patients undergoing screening.

Colposcopy often results in biopsy, which can result in sub-fertility, preterm labor, and perinatal deaths. And so, especially considering this younger demographic, we are concerned about these risks.

The Sponsor states that current U.S. screening guidelines already consider both cytology and HPV 16/18 genotyping to be established approaches to determining which HPV-positive women require colposcopy. In fact, the U.S. Preventive Services Task Force currently gives a D rating for HPV testing in women under 30 because the risks outweigh the benefits from previous clinical trial data.

The Sponsor compares their proposed indication to other algorithms, but only relative to the detection of CIN2 or CIN3. Per 10,000 women, the candidate arm only detected 15 more cases of CIN3 or higher and three more cases of CIN2. The vast majority of women will never develop CIN2 or CIN3, and CIN2 usually spontaneously goes away within two years. These benefits must be weighed against the risks of less screening compliance and adverse pregnancy outcomes.

The comparator arm triages cytology of ASC-US or greater with immediate colposcopy. As the FDA also noted, this is no longer current clinical practice.

Of the patients in this trial, 99% had not received the HPV

vaccine, and the median age was 41, with one-third being postmenopausal. Only approximately 7,000 women were between the ages of 25 and 29. The proposed new indication would pose the greatest risks to young women who hope to have children, so they need to be more carefully studied than what has currently been done.

Lastly, the Sponsor has identified economic and clinical complexities of performing two tests instead of one to justify elimination of cytology. Economic considerations are outside of today's deliberations, but even if they were, HPV tests cost much more than cytology. And the clinical challenge of dealing with more information rather than less is also irrelevant because this proposal often still relies on colposcopy and cytology results as well as HPV results for clinical decision-making.

The data presented here are too discordant with current clinical practice and cannot be used to justify such sweeping clinical change. This proposed indication represents a radical shift in clinical practice which would affect millions of women for most of their adult lives. And so we urge the Committee to consider the risks, especially to young women, the way the indication is currently written.

Thank you.

LCDR ANDERSON: Ms. Elizabeth Jenkins. Is Ms. Jenkins in the audience?

(No response.)

LCDR ANDERSON: Okay. Philip Castle. Is Mr. Castle in the audience?

(No response.)

LCDR ANDERSON: David Chelmow.

DR. CHELMOW: I'm David Chelmow, and I have no conflicts of interest to declare. I am a practicing OB/GYN from Richmond, Virginia, and I'm speaking on behalf of the American College of OB/GYN.

ACOG represents 57,000 practicing OB/GYNs and is very excited about the prospect of things that may advance cervical cancer prevention and screening. It does have four concerns that it wanted me to express, and I'm going to be particularly brief about them because they've already been covered in great detail by other people.

One is we have concerns that introducing a third screening paradigm will cause a huge amount of confusion. We already know that people have not caught on to the new paradigms that went into place two years ago, and actually some of them didn't catch on to the ones that were in place before that.

Secondly, to actually implement these, we would need to develop guidelines, and there are some big areas where there are gaps in data and where there would be some issues developing the guidelines. Some of these are including defining appropriate screening in women 21 to 25, determining the appropriate interval to repeat the test in patients with prior

negative tests -- that's one of the big ones for using it serially that's been brought up -- how to discontinue screening, transitioning people from other algorithms into the screening method.

Although the data here is very compelling, when co-testing was introduced as a preferred method, there were significantly more data, including things like serial screening much further out and randomized trials with two rounds of testing. And we really haven't reached the point where there's this level of data.

And our fourth area of concern is the lack of comparative effectiveness data versus co-testing. The data compared to cytology is very compelling, but as providers trying to decide what the preferred thing for our patients is, it's really hard to know how this stacks up to co-testing. The word "similar" keeps getting used, but whether it is in fact better, not better, or probably a mixture of both, and in what ways of each, really has not been fully defined.

As an additional thing, as an observer, there have been multiple -- you know, the ASCCP management guidelines keep getting put up as being very complicated and this being suggested as a way to simplify them. Because cytology is being used for triage here and we can still get the entire range of abnormal Pap results, as best I can tell, none of those management guidelines go away, and I don't see that this necessarily simplifies things.

Again, thank you for your consideration.

LCDR ANDERSON: Ms. Kate Ryan. Is there a Ms. Kate Ryan in the audience?

(No response.)

LCDR ANDERSON: Ms. Caitlin Phelps. Is there a Ms. Caitlin Phelps in the audience?

(No response.)

LCDR ANDERSON: Ms. Michele Prigo.

MS. PRIGO: Good afternoon. And thank you for allowing me to address the Panel today. My name is Michele Prigo, and I have no financial disclosures to disclose.

I am an HPV survivor, and I'm here to share my personal experience as a women who was spared a stage cervical cancer diagnosis because of the great value of the HPV testing and through traditional cytology screening.

I consider myself one of the lucky ones. It was because of my positive HPV testing results that my normal cytology reading was flagged and I had increased surveillance. This ultimately led to cytology alone indicating that I had low-grade ASC-US, the most minor beginnings of abnormal cellular changes, while colposcopy and biopsy indicated that I had CIN3, the most invasive pre-cancer of the cervix.

If the initial normal cytology reading had not been accompanied with HPV testing, the advanced pre-cancer I was growing would

surely have progressed to stage cancer. I believe that not only would my quality of life have been compromised, but my life itself could have been compromised.

I am lucky because I had a healthcare provider who used HPV and Pap co-testing. In my case, using HPV testing as a primary screening test, followed by a Pap test, would have been just as effective as co-testing, since my Pap was normal. I believe it is imperative that my story not be one of luck, but rather be one of routine. I also believe that every option should be available. All women can be this lucky with the use of HPV testing. This is an enormous step forward in women's health, and it really shows and allows us to look at test results in a more comprehensive way.

We are wives, girlfriends, sisters, and mothers who want and deserve to know our real risk for developing cervical cancer. The capability is there for us. We can be afforded the time to react accordingly before disease progression is beyond medical attention. But this can only happen from availability of all available screening tools.

Thank you.

LCDR ANDERSON: Ms. Deborah Arrindell.

MS. ARRINDELL: Good afternoon. I'm Deborah Arrindell, Vice President of Health Policy for the American Sexual Health Association. This year our organization turns 100, with a couple of name changes along the way. Although I feel 100, I'm actually not quite there yet. And for 18 of those

years, we have had an HPV cervical cancer resource center within our organization.

My statement today is supported by 13 national organizations. These organizations include the Association of Reproductive Health Professionals, Cervical Cancer-Free Coalition, the Foundation for Women's Cancers, The National Coalition of STD Directors, the National Family Planning and Reproductive Health Association, the National Organization for Women, the National Women's Law Center, Planned Parent Federation of America, Reproductive Health Technologies Project, and the Society for Women's Health Research.

Our organizations are deeply committed to promoting and protecting women's sexual and reproductive health. And today we're here to express our support for providing as many tools as possible for preventing cervical cancer, including the option of HPV testing as a primary screen.

There has been a lot of discussion of this already, but the addition of HPV testing to cervical cancer screening has really helped to save women's lives, and the test has proven its significant value in determining a risk for cervical cancer. HPV tests increase detection of common, but very aggressive, adenocarcinomas. They allow better clinical management and reduce harm by more precisely directing appropriate follow-up.

An NCI study in 2009 found that, compared to Pap testing alone, using an HPV test for primary screening with triage to Pap increased

detection of significant cervical pre-cancers by 30%.

Our organizations support HPV primary screening as an additional option for healthcare providers. We are not ourselves equipped to say that it's better than another form of testing. We believe that all the options should be available and that providers and women should be able to make the best decisions around what is best for the patients in those circumstances.

We rely obviously on the professional judgment of the societies such as ACOG, the American Cancer Society, the USPSTF, and we urge this Panel to make all products that are safe and effective for cervical cancer prevention widely available.

We very much appreciate the opportunity to make a statement today, and we would welcome an opportunity to further discuss this.

Thank you.

LCDR ANDERSON: Mr. Keith Gantner.

MR. GANTNER: Good afternoon. My name is Keith Gantner. I am a senior vice president at Hologic Diagnostics.

As most of you know, Hologic manufactures and markets the ThinPrep Pap test imaging technology and two HPV tests that are currently FDA approved. We'd like to thank the Panel for giving us the opportunity to present today. As we look to the future, Hologic recognizes that HPV primary may have a role in screening.

I'd like to start by framing up the current state of cervical cancer screening in the U.S. For several years now, current guidelines indicate that the preferred method for screening is the utilization of both cytology and HPV testing. And a majority of physicians in the U.S. utilize this screening algorithm today for women 30 and older. This proposed indication would require the physician to maintain current practice by collecting the same sample from the patient but choose to receive one result, being HPV, when they currently have the option to receive two; essentially the same collection procedure, except the physician and patient would receive less information than what they currently get today.

With this current state as the backdrop, we are here to present a few critical items for the Panel's consideration.

Point Number 1: Will the adoption of the candidate indication lead to significant missed cancers, in comparison to the current screening and management paradigms?

The second point: The two comparators that are the focus of this application do not reflect current clinical practice and seemingly disadvantage cytology and co-testing performance.

So Point Number 1: In the risk for missed cancers, as Dr. Wright noted earlier, due to the low prevalence of cervical cancer in the clinical trials, it's difficult to assess how a new screening paradigm would impact cervical cancer detection. As a result, can the Panel be certain we will

not see an increase in cervical cancer incidence and mortality with the removal of the Pap test as the frontline screen?

For example, in the current ATHENA study, it's our understanding that only 27 cases of cancer were evaluated among more than 47,000 enrolled patients. Clearly there's a need for more data. Also, knowing that the retrospective analyses of co-testing patient populations suggests that the largest loss in sensitivity, if we were to move to primary HPV, will be at the cervical cancer endpoint.

Co-testing data from 330,000 women in the Kaiser population found that removing cytology from the frontline screen would miss a statistically significant 10.3% of cervical cancers. I recognize that there's been additional data from Kaiser presented today that should be part of the discussion as well.

We also understand that a major national laboratory submitted a statement to the Panel today with an analysis of 3.7 million women who received a co-test, although yet it unpublished the data that demonstrates a 13.5% missed cancer rate by removing cytology from the frontline screen.

In regards to Point Number 2, the comparator and age considerations, we recognize that it's not the responsibility of the Panel to establish guidelines for medical practice. But knowing that the main comparator, based on the 2006 consensus guidelines, did not include HPV as a reflex to ASC-US cytology to determine referral to colposcopy, we ask that

further analysis in addition to the comparator be considered. We feel it's important to understand performance relative to what's actually happening in clinical practice, especially as we consider HPV testing in a younger population.

The alternate comparator referred to earlier today by Roche is that co-testing or co-testing hybrid is not a direct comparison of the current co-testing indication. We know that more than 50% of women age 30 and older are tested with both HPV and cytology. Is the Panel comfortable that there is enough data to justify HPV screening beginning at age 25?

We feel it's important to consider a comparison of the proposed primary HPV indication to co-testing in an apples-to-apples analysis starting at the same age of screening. Although these analyses have been included in the appendix, we ask that they be considered, as significantly more disease is detected at 25 and 30 as compared to the proposed primary HPV indication.

In closing, we understand and empathize with the complexity of the data and the significant implications of the questions before the Panel. We feel the current analyses are underestimating the contribution of cytology, which has been one of the most successful screening programs in the history of the United States and central to the reduction of cancer. We are concerned that the implication of removing cytology as part of the primary screen and changing the age of initiation of HPV screening is not fully

understood and may result in significant clinical implications, including increased colposcopy rates in the younger population and missed cervical cancers.

LCDR ANDERSON: I'm double-checking. Is Ms. Elizabeth Jenkins available?

(No response.)

LCDR ANDERSON: Mr. Philip -- yes?

DR. WASSERMAN: I'm not Elizabeth Jenkins, but I represent the CTC and the ASC, so I believe it should be -- if you allow me, I'm Dr. Wasserman. I'm the director of cytology at Columbia University. I am representing the Cytology Education and Technology Consortium, and I was paid for my travel. And I really appreciate you listening to me.

So the CTC is an independent consortium of professional organizations involved in diagnostic cytopathology. The member organizations are the American Society of Cytopathology, the American Society for Clinical Pathology, the American Society for Cytotechnology, the College of American Pathologists, The International Academy of Cytology, and the Papanicolaou Society of Cytopathology. And the representatives and presidents of all these organizations are nationally recognized members of the cytopathology community.

The CTC would like to bring to your attention four main concerns that may potentially impact safety and efficacy for cervical cancer

screening in the United States, if HPV primary screening is approved by the FDA.

First, quality control. As laboratorians, we are highly concerned about appropriate test quality control. In the Roche package insert for the current cobas HPV Test approval, information regarding specimen adequacy, internal control for epithelial cellular components, and potential interfering substances is limited. This should be evaluated in the package insert for this PMA. Laboratories should be cautioned that they need to perform verification, validation, and continue to monitor quality assurance, as warranted, for HPV testing.

In our opinion, there is a risk of false negative HPV results without the added morphologic control offered by co-testing, because the platform lacks a control mechanism that specifically identifies the DNA of epithelial cells as opposed to other contaminant cells.

Concern Number 2, HPV-negative cervical cancer. As with any other lab test, the sensitivity of HPV testing is not 100%. A subset of carcinomas, both squamous and glandular, and other tumor types may not be detected by HPV testing. As found in the recently published United States Cancer Registry study, 9.4% of cervical cancers were HPV negative and an additional 3.2% contained rare HPV subtypes. As with most cancer, clinical outcomes are better when cervical tumors are detected at a lower stage, and we are concerned about delayed diagnoses resulting in higher-stage tumors

due to longer screening intervals after negative HPV results.

Concern Number 3, HPV testing methodology. If FDA approval is granted for the Roche test, clinicians will very likely equate all HPV tests. However, individual laboratories use different HPV testing platforms, including laboratory-developed tests. As laboratorians, we stress that primary cervical vaginal screening by HPV testing should be performed using HPV tests that FDA approved for primary cervical cancer screening and should not rely on tests that are not approved for the specific indication of primary HPV screening. The testing labs should be cleared and approved and participate in regular proficiency testing. Clinicians should be advised to inquire about the HPV testing in their labs.

And Concern Number 3 [sic], triage of high-risk HPV-positive patients. Before primary HPV screening for cervical cancer is adopted, there should be clear evidence-based algorithms for the follow-up of positive and negative tests to prevent loss of women to appropriate follow-up and potential increases in cervical cancer incidence.

The prevalence of high-risk HPV types varies with demographics of populations, and the current-use population is very diverse, in contrast to the patient populations in the prior European trials. As found in the recently published U.S. Cancer Registry study, 12.6% of cervical cancers are either HPV negative, 9.4%, or contained rare HPV subtypes, 3.2%. Due to the documentation of HPV-negative squamous cell carcinoma and

adenocarcinoma, women should have a morphologic examination in their screening history and should not be screened solely --

LCDR ANDERSON: Mr. Philip Castle.

(No response.)

LCDR ANDERSON: Ms. Kate Ryan.

(No response.)

LCDR ANDERSON: Ms. Caitlin Phelps.

(No response.)

LCDR ANDERSON: And Patricia Wasserman is a walk-in. Okay, we got it. Okay.

DR. CALIENDO: I'd like to thank all of the speakers.

Do the Panel members have any questions for the presenters?

(No response.)

DR. CALIENDO: Okay. Then I pronounce the Open Public Hearing to be officially closed.

Okay, we will now continue to the Panel deliberations. As a reminder, although this portion is open to the public observers, public attendees may not participate except at the specific request of the Panel Chair. Additionally, we request that all persons who are asked to speak identify themselves each time so that the transcriptionist can collect all the information.

Based on this morning, we have some questions to go back to

for the Sponsor and to the FDA. So I don't know if the Sponsor would like to speak first.

DR. MAJEWSKI: Thank you very much. Christoph Majewski again.

So there were a number of outstanding questions from this morning that we briefly would like to address. I guess the one thing that I would personally like to address first is the question about the European studies, why they did not consider 25.

So as was discussed, HPV prevalence in younger women is particularly high, and at that point in time the tool of genotyping was not available in all of the European studies. So all of these studies have been only conducted with high-risk wound testing, and the only reflex tool available was cytology. So that was one of the decisions not to go after the younger ages. But it needs to be noted that in the UK, the age of 25 is considered, in the future, as a potential lower limit of primary screening.

So with that said, I would like to ask Dr. Behrens to present to you the question on the demographics in the follow-up study. That was one open question. And she will also talk about the performance of our algorithm in the Hispanic population and be following up with the performance in 25- to 29-year-old, which was a question coming up in the FDA session. We have some more details that we would like to complement that with and provide you some more detail on that, and then follow up with information on the

HPV 12 high-risk positive in the NILM population, 25 to 29 and older, and finally close out with random biopsy, first by Dr. Behrens and then Dr. Tom Wright will follow-up about clinical practice for random biopsy.

DR. BEHRENS: Thank you. This is Catherine Behrens.

Slide up, please. In answer to Dr. Saraiya, who wanted to see the demographics of the follow-up population, we have that here. And keep in mind that this is the population that went into follow-up after having colposcopy, but less than CIN2 diagnosis. So most of these women would have had either an abnormal Pap or HPV positive, except for the small randomized group of negative/negatives.

So you can see that the median age is lower than it was in the total population; it's 38. And, again, that reflects that these are predominantly women with abnormal results. And this again emphasizes the fact that cervical cancer is a disease of younger women. We also see that, in the distribution of the age groups, there's a slight shift towards a younger population.

In terms of race, there's a slightly lower percentage of white women and a slightly higher percentage of African-American women. And, again, this is because the prevalence of HPV is slightly higher in African-American women. And, in ethnicity, the Hispanic population was approximately 19.6%, and again slightly higher than what we saw in the overall population.

Okay. And I think there was also a question about the performance in the Hispanic population. Yes, okay. Slide up, please. Okay. And this just shows the relative sensitivity and specificity of the candidate to cytology in Hispanic population, and you can see again that the performance of the candidate algorithm is much improved over cytology, and the relative sensitivity and specificities are approximately the same. The PPV again, you know, within the difference of numbers, because there was a smaller number of Hispanic women in the population, there's no difference between this and the white population and the overall population.

Okay. All right. Then, I think, next we have some data in the 25- to 29-year population. Slide up, please. This slide shows the relative performance in the 25 to 29 age group as well as in the over 30 age group, and you can see that the sensitivity of the candidate in the 25 to 29 age group is 1.66, and that's actually higher than it is in the overall population. And in the over 30 population it's 1.26 relative to cytology. So again the candidate is outperforming cytology in sensitivity, and specificity is slightly higher in the over 30 population, but essentially the same in 25 to 29.

Next slide, please. If we look at the other performance parameters for the 25- to 29-year age range, we see that again the PPV, NPV, PLR, NLR for a CIN2 or greater compared to the comparator is again higher and all the differences are statistically significant.

In the next slide we can also take a look at the clinical resource

utilization in that age range, and we see that the candidate is highlighted, and you can see that although the number of colposcopies increases, the number of disease detected also increases. So the ratio of colposcopies to CIN3 cases detected is actually lower than the comparator as well as ASC-US triage and the co-testing hybrid.

Okay. And this is just to support the data that the FDA had already shown. We can also show the data that we have for the random biopsy. And, again, as Dr. Kondratovich said, this is still under review with the FDA. Slide up, please. We see in the top rows the results of the relative sensitivity and specificity of the candidate compared to the comparator for the directed biopsy only, and you see it's essentially the same as it is for the directed and random combined, which is what we reported out this morning in the study.

Okay, next slide. And then we can also see the other parameters, PPV, NPV, PLR, and NLR. And again we see the superior performance of the candidate for each of the parameters, and it's the same for the directed versus directed and random combined. Okay.

DR. MAJEWSKI: Why don't you also comment on HPV risk categories?

DR. BEHRENS: Yes. I thought Tom was going to say something.

DR. WRIGHT: Talking point up, Sean.

The discussion came up this morning about random biopsies.

When we began designing the ATHENA trial, there were a number of publications from relatively large studies clearly showing that a random biopsy increases the sensitivity of colposcopy by 25% to 33%. Because of these studies, there is a growing awareness in the colposcopy community about the use of random biopsies. Dr. Walter Kinney, who spoke earlier about the Kaiser guidelines, in Kaiser, now they recommend four-quadrant biopsies at the time a colposcopy is always done, but that is the recommendation. I understand why many senior colposcopists do not feel the need to do that. They've gotten lots of experience.

Having said that, though, in the most recent addition of the American Society of Colposcopy and Cervical Pathology's textbooks, it recommends taking more than one biopsy. There is a long discussion about four-quadrant biopsies. It doesn't recommend four-quadrant biopsies, but this awareness is increasing. And as you saw from our data, there is no difference in the performance of the candidate algorithm versus the comparator, whether we only look at directed biopsies or whether we look at both.

Thank you.

DR. MAJEWSKI: So we actually left out the data on the performance in the different risk categories for the 25 to 29 group, and I ask Dr. Behrens to present those data to you.

DR. BEHRENS: Slide up, please. There was a question this

morning about the 12 other positive/negative cytology that would be deferred, and if you see on this slide, that's what's highlighted. And in the 25 to 29 age group, that would be 10.6% of that age group versus approximately 5% in the over 30 age group. And you could also see, for the other genotype categories, the referral and for HPV negative as well.

Thank you.

DR. CALIENDO: Thanks. Does the FDA want to present anything else, or are you satisfied with what they've presented?

We're not to the discussion questions. Oh, you want to present the discussion questions? Why don't we -- you want to do that before we ask additional questions?

Okay. To the Panel. This is your opportunity to ask the Sponsor anything that you would like to ask. And we will have an open deliberation and then after break we will go through the questions that the FDA has posed to us. So now is the time to ask anything of the Sponsor, and I would say, anything of the FDA also. Go ahead.

DR. UNGER: This is Beth Unger.

I was wondering if you had a comment about the histologic classification that was brought up, the question about the validity and where that other number came from.

DR. MAJEWSKI: Christoph Majewski.

So you're asking basically about the adjudication of the

histology, which was done by standard pathology review. And there were some reports from recent publications about p16 data, so we certainly can present the adjudication and how that impacted the results. And I would ask Dr. Wright to come up. I'm not sure whether we have the data for p16.

DR. WRIGHT: Tom Wright.

The data which was presented during the open discussion is from a published paper. It is the second of the ASC-US triage papers, which we have.

And I'm sorry, it's a new slide, Sean, that just got made. I can read it. I can give you a rough idea. I'm sorry, we made a slide for it.

We had 77 cases of CIN2+ in women 21 years of age with ASC-US. Okay, so 21 and older with ASC-US, a total of 77 cases. Eight cases were high-risk HPV negative. We found that there was a higher rate of high-risk HPV-negative cases in older women than younger women. So one of the things we wanted to do was to evaluate the validity of the adjudicated pathology diagnosis.

All biopsies were read by two GYN pathologists. If we agreed 100%, we had a locked diagnosis. If we disagreed, it blinded to a third GYN pathologist. If we had a three-way disagreement, everything was read in consensus and everything was read blinded to HPV status and to age.

Among these eight cases that were high-risk HPV negative of CIN2 or greater, three occurred in women 40 years and under. One had HPV

82. That one was p16 positive. The other two were p16 negative. Five cases occurred in women over the age of 40. Three of those were p16 negative. That is a total of five cases out of 77 cases for p16. We did not test the other cases, though, for p16. It was only a separate adjudication.

Is that clarifying?

DR. WRIGHT: Thank you.

DR. CALIENDO: Angie Caliendo.

I'm actually still a little confused because I'm going back to what -- I think it was Dr. Austin who said that a large percentage of them were misclassified.

DR. WRIGHT: Of the ones that were done with p16, but that was only a small subset of the cobas HPV-negative cases because we didn't do p16 on all of the cases. We only did it on the ones that were cobas HPV negative.

DR. CALIENDO: Okay.

DR. WRIGHT: And of the ones that were done, it was a large percent. But that was a small subset.

DR. CALIENDO: Of the total CIN+?

DR. WRIGHT: Of the total.

DR. CALIENDO: Okay. Go ahead.

DR. WAXMAN: I have a very basic question on the cobas test itself. Is there a viral load threshold that determines that a test is positive or

negative? Or is it p16? Any HPV that's detected becomes a positive result? So that's part one.

Part two is a concern that's been brought up by several of the questioners about laboratory-developed tests. Currently there are labs out there that are selling p16 -- that are selling PCR testing and are using it or promoting it for use in co-testing, and I'm very concerned that if we approve this for primary screening, laboratories will do the same thing with a product other than yours.

DR. MAJEWSKI: So most importantly, p16 is not part of our submission.

DR. WAXMAN: No, no.

DR. MAJEWSKI: None of the data have used p16.

DR. WAXMAN: I'm not talking p16. HPV 16. I'm sorry.

DR. MAJEWSKI: So when you look at -- your question basically is about how we determined the cutoff --

DR. WAXMAN: Yes.

DR. MAJEWSKI: -- of the HPV test. So the cutoff was actually determined in the first part of the study, the cross-sectional part of the study, and it was actually set for the detection of CIN2+, and the claims that we were targeting at that point in time was the ASC-US population and the HPV co-testing. So the clinically relevant cutoff was for CIN2+, and the same cutoff was applied now for the primary screening.

DR. WAXMAN: But there is a viral load threshold.

DR. MAJEWSKI: You might say that, but I need to emphasize that this is not a quantitative test.

DR. WAXMAN: Okay, sure, I understand. Thank you.

DR. CALIENDO: Go ahead.

DR. BLUMENSTEIN: This is Brent Blumenstein.

I wanted to ask a couple questions about the verification bias adjustments. The first is I have no sense, or at least I haven't been able to dope it out, of how many cases induced the need for verification bias adjustment. Can you show me that?

DR. MAJEWSKI: So you would like to see the number of cases that induced the need for verification bias adjustment?

DR. BLUMENSTEIN: Yes.

DR. MAJEWSKI: I would ask Dr. Sharma to come up to answer that question.

DR. SHARMA: So can I ask a clarification? What do you mean by how many cases?

DR. BLUMENSTEIN: How many cases did not have colposcopy results by method?

DR. SHARMA: So we had approximately 1,073 women who were invited to colposcopy, and we have the disease verification on those 8,073. And then the population itself is 40,944.

DR. BLUMENSTEIN: But how many were test positive and missing colposcopy results and how many were test negative for each of the methods? I assume that it's the same for the comparator and the candidate method; is that correct?

DR. SHARMA: No, it will be different. Comparator is just the Pap test, which is Pap negative. So if you're asking just the Pap negative figure --

DR. BLUMENSTEIN: But the total would be the same; is that correct? I'm just trying to get a good sense for how it is that you ended up implementing the verification bias adjustment.

DR. SHARMA: So basically how many cases of -- I'm asking you a question again. How many HPV-negative cases?

DR. BLUMENSTEIN: Let's just take the candidate first.

DR. SHARMA: Okay.

DR. BLUMENSTEIN: So how many test positive were missing colposcopy?

DR. SHARMA: It looks like Marina wants to --

DR. KONDRATOVICH: Okay. So let me clarify this data, what we have. So we have the study design when we have cytology positive and like HPV positive. Theoretically, all women who have at least a cytology positive or HPV positive needs to go to colposcopy. When we checked data, it was around maybe like 90%, 93%.

So this cell has some verification bias, but of course it's relatively small. The biggest verification bias is the fourth cell, where you have cytology negative and you have HPV negative. Then in this cell we have 854 subjects with colposcopy results. And so they were verified, and because they were random, we can impute results based on the HPV, cytology, and additionally age. So verification bias, it was slightly different, of course, for the cells. So when you have positive, it's close to 100. I checked. It was like 85%, 93% in the cells. But, of course, for the negative, it was like around, I think, 3.8%. Yes?

DR. BLUMENSTEIN: I'm sorry, say that again. How many percent?

DR. KONDRATOVICH: Around, I think, 3.8%. Around 4%.

DR. BLUMENSTEIN: For the test positives?

DR. KONDRATOVICH: Yes, because it was around 32,000 subjects with this cell.

DR. BLUMENSTEIN: All right. So for test negative, how many?

DR. KONDRATOVICH: Yes.

DR. BLUMENSTEIN: What percent was it?

DR. KONDRATOVICH: Yes, around 3.8% randomly selected subjects, but the absolute number of the subjects, it was 852.

DR. BLUMENSTEIN: Okay.

DR. KONDRATOVICH: So it was relatively big.

DR. BLUMENSTEIN: And it was a key assumption here that this --

DR. KONDRATOVICH: Yes.

DR. BLUMENSTEIN: -- missingness is at random.

DR. KONDRATOVICH: Yes. Um-hum.

DR. BLUMENSTEIN: What assessments did you do to convince yourself that it was?

DR. KONDRATOVICH: Yes, okay, we can joint.

DR. SHARMA: Missing at random assumption was verified within each subgroup using demographics and HPV values.

DR. BLUMENSTEIN: And you had no reason to think that you had anything but missing at random; is that correct?

DR. KONDRATOVICH: Yes. Usually in these three cells where theoretically we need to have everybody with colposcopies because everybody was invited, but we did not have colposcopy for everybody, so we checked with covariates and only covariates, of course, like usually in statistics which we collected, which we think is important.

DR. BLUMENSTEIN: Um-hum.

DR. KONDRATOVICH: And it was like -- looked like it doesn't depend on the missingness completely like at random. When we are speaking about the fourth cell, when cytology negative and the Pap negative, here it's like even true way of checking. First, these people initially were

selected randomly. We tried to consider that they're exempt. Even we obtained the results. The Sponsor checked really that you don't have any pattern in covariates.

DR. BLUMENSTEIN: Was the clinical site or class of clinical site included in that assessment for randomness?

DR. SHARMA: That was not included.

DR. KONDRATOVICH: You mean collection site or laboratory testing site?

DR. BLUMENSTEIN: Well, I mean, in other words, was there a class of sites, say, an academic site, for the -- there was more missing colposcopies or something along those lines? Or was there a deviation from randomness of missing due to sites or class of sites?

DR. SHARMA: No, we did not use site as a criteria to verify missing at random. When you use HPV values which are very, very consistent across sites, it basically takes care of any site variation.

DR. BLUMENSTEIN: So this really kind of leads me to another kind of question, and that is that you argued that you have a representative sample of the individuals in the -- you've shown slides to that effect. But yet there's a statement in your briefing book that says that you precluded referral clinics.

And so I'm just wondering whether the representativeness that you are talking about is somehow or another diminished as a result of you

excluding referral clinics. Since I don't practice this, I just need to know what that means. I mean, in other words, what is a referral clinic versus the kind of site that you included?

DR. KONDRATOVICH: Yes, let me clarify that when we speak about referral clinic, it's more like colposcopy clinic. It's the places where women already have referred to do some kind of colposcopy procedure. But this test, all of this test, is for the doctor offices, that you need to include all women who are going to the doctor. It's not the women who are already sent to the colposcopy clinic. Otherwise it will be severe bias.

So this study is really unbiased with regard to intended-use population because this is a test for the doctor office, not for the women who are already sent to colposcopy clinic. So here referral is more colposcopy clinic, women already sent to have this procedure and definitely were not included. Otherwise it will be biased population.

DR. BLUMENSTEIN: I have to actually ask the rest of the Committee members. Am I just being concerned about this because I don't know the field, or is this of concern, that the kinds of recruitment that were implemented might make a non-representative population?

DR. KONDRATOVICH: So this test can be used in colposcopy clinic in order to make decision, because they already made decision to send to colposcopy, yes? So this test is really for the doctor office, when it will make decision whether this woman needs to go to colposcopy or not.

DR. CALIENDO: Angie Caliendo.

I think the way it was designed was for the primary care -- they're doing the testing where the primary care is given, not where the referral is given.

Go ahead, Ken.

DR. NOLLER: Yes, they were looking at screening. If somebody already has an abnormal Pap, refer to colposcopy clinic or a gynecologist because of the abnormal Pap. They didn't include those. So that wouldn't be screening; that would have been diagnosis or evaluation. So I think it's appropriate the way they did it.

DR. CAIN: So I have a question out of curiosity. For the 25 to 29 age range with the HPV testing, 704 were referred to colposcopy compared to 780 in the other arms. It really isn't colposcopy that raises the issue of harm. It's whether or not they move forward to LEEP or to some other form of treatment. So I'm curious. Since we're missing that data, how many did, and is it different in that group than the rest of the groups studied?

DR. MAJEWSKI: So you're basically -- sorry, Christoph Majewski again. And your question is about whether there was a difference in the group 25 to 29 who were sent to colposcopy clinic and then had a LEEP procedure compared to the overall population?

DR. CAIN: Yes, it's the LEEP procedure I'm focusing on.

DR. MAJEWSKI: Okay. So can I ask Dr. Behrens to come up?

DR. BEHRENS: Catherine Behrens.

Since the patients exited the study if they had CIN2 or greater, we don't have a lot of information about treatment. The treatment was up to the decision of the investigator, the OB/GYN who initially saw the patient. So we don't have that data.

DR. BIRDSONG: George Birdsong.

This is also for the Sponsor. I think this question actually has already been answered. I just want to clarify it. And this is getting back to Dr. Austin's presentation and the p16 performed on a subset of the biopsies.

So the question in my mind here is, if p16 was performed only on the patients who had been HPV negative, you know, on the one hand it may not be surprising that you had a fairly high rate of p16 negatives. But if I understood it correctly, it was not performed on any of the patients who were HPV positive. On the one hand you might expect to find a higher rate of p16 positivity, but do we have or not have that data? Because if you found a similar rate of p16 positivity, then that would suggest that maybe the biopsies were read more aggressively than commonly occurs. So it would be nice to have some clarity on that.

DR. MAJEWSKI: So your question is, when we perform p16 testing in the samples that were missed HPV, whether we included also a subset of HPV positives?

DR. BIRDSONG: Right. And that gets back to my question this

morning about control and adjudication of the biopsy reading process because that seems like a good way to do it.

DR. MAJEWSKI: Sure. So Tom.

DR. WRIGHT: Tom Wright.

Dr. Birdsong, we did not, as part of ATHENA, do p16 staining. The gold standard was histology. What you saw was a post hoc analysis to try and figure out the missing cases. As part of other studies looking at adjudicated biopsies from ATHENA, we have wider p16 immunostaining on cases with adjudicated diagnosis of CIN2 and CIN3, and the data is exactly what you would expect coming from Dr. Mark Stoler's laboratory. He has published this data. High 80% for CIN2's, 90% for CIN3's. This is really a small subset to find out why we had HPV-negative CIN2 or greater lesions.

Is that clear?

DR. WRIGHT: Thank you so much.

DR. BLUMENSTEIN: So I don't know whether I feel obliged to ask statistical questions. All right. So as I understand the general analysis, it was done for the comparator and the candidate, as if those were independent samples. And what I'm wondering is, did you do analyses in which you didn't assume -- because the results came from the same patient, the paired results, did you do analyses where you didn't make the assumption of independence?

DR. MAJEWSKI: So your question was -- this basically reads,

targeted at whether we have any analyses -- despite we did all of the testing from the same sample or from the same patient, whether we have any modeling around that?

DR. BLUMENSTEIN: Yes. Did you assess the -- I mean, you obviously assumed and felt it was okay to do these as independent samples.

DR. MAJEWSKI: Um-hum.

DR. BLUMENSTEIN: But did you do an assessment to find out if there were different results when an assumption --

DR. KONDRATOVICH: No, we don't make any assumptions that result statistically independent, because we have the patient, and for this patient we have some samples from the sample. There are two results. So in all calculations, when you need to construct confidence interval for difference, correlation, of course, was incorporated. So we don't consider that they're independent.

So every time when you see difference between performances, correlation was included. Because you're right, this is peer study design, how we call it statistic, that every patient has results of their candidate method and the comparator, and when we calculated difference, of course correlation was included in this calculation. Otherwise calculation can be wrong.

DR. BLUMENSTEIN: Well, I mean there are statistical models that don't assume independence, that take into account --

DR. KONDRATOVICH: But here, because we have the same patient and their candidate and comparator, a lot of cells are similar. Of course, this performance, the data should be considered like correlated.

DR. BLUMENSTEIN: So the answer is you didn't do a model that allowed for the estimation of the correlation of the results between patients?

DR. KONDRATOVICH: Yes. Of course, in the estimations, it was included already, model that correlation that this comparator and candidate, they're correlated and all calculations included this correlation. To consider that they're independent, this is not really reflecting this type of the structured data. So this analysis, we're considering like it's not clear what kind of information we can obtain if we know that they are correlated. And in all calculations, correlation was included.

DR. BLUMENSTEIN: Maybe this can be taken off on.

DR. RAND: Ken Rand.

I would like to get some clarification on the sample type that would be included by standalone molecular testing. Would that always be a sample obtained in a physician's office under conditions, you know, similar to or the same as what you would do for a Pap test? Or could this open the door to patients self-testing and sending the specimens in directly to whatever lab they chose?

DR. MAJEWSKI: All of the samples -- and this is Christoph Majewski again. All of the samples in the study were collected in preservative

media and were actually collected by a physician or healthcare professional. And so our claims do not go beyond that.

DR. SIMON: The FDA approval would be explicitly for this sample type and this test. So it would not -- you know, the approval of this test for this indication should not be applied to other tests or other sample types.

DR. WAXMAN: Another very basic fundamental question. Going back to the baseline ATHENA study, as I read it and reread it, one of the things that kept hitting me in the face is that the HPV test that was used to determine positive or negative was not the cobas test. It was Linear Array and it was Amplicor. Could you discuss that a little bit?

DR. MAJEWSKI: Yes, that is correct. So, in fact, when we designed the ATHENA study, we wanted to have a most thorough assessment of the HPV positives in the total ATHENA population. Amplicor and Linear Array are both highly sensitive tests, analytically sensitive tests, so that would pick up any of the virus in the population. And both together actually include 16 high-risk genotypes.

So from that perspective, we really created a complete inventory of HPV positivity in the population. So we expected, from the beginning, that cobas positives would only be a subgroup of the Amplicor and Linear Array positives because, first and foremost, it uses a clinical cutoff for CIN2+, but secondly, it also only has 14 high-risk genotypes included.

DR. WAXMAN: So you then went back afterwards and reanalyzed it using the cobas?

DR. MAJEWSKI: That is correct. So all of the data that you see, just look at the cobas positives and basically assess them Amplicor and Linear Array positives, cobas negatives, as missed samples by the cobas test.

DR. CALIENDO: Just a reminder to state your name before you speak. Also we have Dr. D'Agostino on the phone, and I want to give you an opportunity to make comments, ask questions.

DR. D'AGOSTINO: Is it all right to do it now?

DR. CALIENDO: Yes, go ahead.

DR. D'AGOSTINO: Can you hear me? Can I be heard?

DR. CALIENDO: Yes, go ahead.

DR. D'AGOSTINO: Okay. I've been in an awkward position here trying to keep up with all the material and what's going on. I want to thank the presenters for having such clear presentations. I was able to follow it.

I think in terms of the question of the independence that was asked a moment ago, I don't think that they have a real issue with that. I mean, with the way they ran the study and the methods they employed --

DR. CALIENDO: I'm sorry, can I interrupt for a second? Are you on speakerphone?

DR. D'AGOSTINO: No.

DR. CALIENDO: Okay, because you're a little garbled. So you're

on a handheld?

DR. D'AGOSTINO: I'm on a handheld.

DR. CALIENDO: Okay.

DR. D'AGOSTINO: I'll speak slowly, so please let me know if I can't be heard clearly.

Okay, with regard to the methods they used, I think they're a very impressive set of statistical methods that back up what they're presenting, and a question which we'll come to later on is, are they really doing an effectiveness type of study which would sort of be needed to make the statement of change making or changing practice and what have you? But I think their data are quite substantial, and I wanted to make sure I responded to the question that was asked about the independence and the dependence.

I think their analysis, if I hear it correctly and read it correctly, that they have covered themselves very well in that respect, and I think we cannot worry about that. There are other things in terms of generalizability and how this impacts on practice and so forth, and I'll hold those comments off until they come up.

Thank you for recognizing me.

DR. CALIENDO: Other questions? Go ahead.

DR. SCOTT: Cherise Scott, the Consumer Rep.

I'm just trying to understand. I got the argument around the

weaknesses of cytology just alone and then the strengths of primary HPV, but I don't really get your arguments against doing the co-testing. So I would think, can you just kind of clarify exactly why that wouldn't be an option?

DR. MAJEWSKI: So co-testing certainly is an option; it is an option in the current guidelines. And our data show, when you look at the algorithm, ATRI NM 30GT, that is basically co-testing using the option of genotyping that is given in the current guidelines. So we compared to co-testing, and we show that we have equal performance compared to co-testing. So there's nothing against co-testing. We just think that the cobas test should be equally approved for the primary screening indication because it shows the safety and effectiveness similarly like co-testing.

DR. WAXMAN: This might be an FDA question, but -- I'm sorry. Alan Waxman.

DR. KONDRATOVICH: Let me --

DR. WAXMAN: Okay.

DR. KONDRATOVICH: I apologize.

DR. WAXMAN: Okay. This is not Alan Waxman.

DR. KONDRATOVICH: Yes, Marina Kondratovich.

So in the presentation, FDA presentation, we have a table for benefit/risk analysis, for example, for 10,000 patients, and one of the lines is exactly this co-testing. And because of the lack of time, I was discussing only candidate versus comparator. But if you look at your slide, like 52, then you

see these results, and you can see what is the number of colposcopies, what is the true positive, and this is like true positive for CIN3, true positive for CIN2, all of this data.

DR. CALIENDO: That's Slide 52.

DR. KONDRATOVICH: Yes.

DR. SIMON: And I'd also like to add a little clarity, that when I say the approval would only apply to the specimen type, that would exclude self-collection because a self-collected sample would be considered a distinct specimen type.

DR. WAXMAN: Alan Waxman again. And don't go too far from the podium because my question is that every patient in this study had a cervix. Will the labeling be specific that this test is not to be used for patients without a cervix? Post-hysterectomy.

DR. SIMON: We would mention that the test has not been evaluated in women without a cervix. And we could take it upon advisement to include a specific counter-indication or not, or just mention that it hasn't been evaluated.

DR. WAXMAN: Thank you.

DR. BURK: So I have a question that -- Robbie Burk. So I think the analysis has been very comprehensive. I think you dealt with the validation bias with the added information that HPV will add to the cytology and how that will change things.

I'm just struggling with the issue of the age, I guess, in your proposed new indication, when you say women 25 years and older, et cetera, et cetera, but you don't mention the vaccine. And I brought it up again, and I don't have the answer, but I'm just concerned that HPV is higher in younger -- HPV 16 particularly is higher in younger women, and you showed in your study almost threefold higher in the women less than 30 versus older than 30. Many of the cytologic abnormalities or disease is caused by that. And if we have to make -- you know, if we have to make this decision, one is that your indication doesn't mention whether they've been vaccinated or not vaccinated. And I don't know. I just feel I need some more discussion and thinking about changing this age, that as we move forward, how that's going to affect really the safety, the performance of women, particularly in that younger age group.

DR. MAJEWSKI: Christoph Majewski again.

So first it needs to be noted that in ATHENA itself, only less than -- I'll speak louder. So in ATHENA itself, only 2% of the women had actually been vaccinated. Less than 2%. But as it regards to impact that vaccination will have on the performance of the candidate algorithm, I would ask Dr. Behrens to come up and speak to it. That's all right.

DR. CALIENDO: I'm sorry, I couldn't hear about what you said about who had been vaccinated. I'm sorry.

DR. MAJEWSKI: Only 2% of the women in ATHENA had a

vaccination.

DR. WRIGHT: Tom Wright.

Dr. Burk, we simply don't know what is going to happen with vaccination, from my opinion, either on cytology performance or on HPV testing or on co-testing. I showed the slide earlier about what we know will happen. We will get reductions in HPV, we'll get reductions in CIN2 and 3, we'll get specific reductions in HPV 16/18 associated CIN2/3. All of those will impact the performance of any screening test. And the only way I know of, other than to do observational studies over time, which many groups are trying to do -- the CDC is looking at this quite carefully -- is to do modeling studies, and I don't know of modeling studies which have looked at HPV screening in this age group. So I have no additional information. Sorry.

DR. MAJEWSKI: Christoph Majewski again.

I just need to correct it. It was 1.2%. I got the number wrong. So thank you, Dr. Kondratovich.

DR. NOLLER: Ken Noller.

Just for interest, in the age group 25 to 29, what was the percent vaccinated?

DR. MAJEWSKI: In the age group 25 to 29? Do we have that breakdown? So the question specifically is, what is the vaccination rate in the age group 25 to 29? I don't think that we have that information available. We can see whether we can make it available in the course of the day.

DR. HARRELL: Lizzie Harrell.

So if you don't do something like co-testing, if you start -- if the vaccine is becoming more prevalent now, if there is a change and it would affect the HPV test, how would you know that if you aren't doing some longitudinal studies along the way?

DR. SIMON: Kate Simon.

To address the previous question, the 1.2% based on the timing of the study and the timing of the vaccine approval, that 1.2% most likely would all have fallen within that age range, the 25 to 29. But the company can verify that for us.

DR. MAJEWSKI: So sorry. Your question was specifically about what is the impact of the genotypes in the vaccinated population?

DR. HARRELL: Well, this was in general, but mainly it had to be the other one because the test is just really becoming more prevalent now. But my thing is, if it is going to affect the HPV test, if you aren't doing some comparator testing at the same time, how would you know if the HPV test does not work as well once you start using it? Look at tests of the patients that have been vaccinated for HPV?

DR. MAJEWSKI: So I will ask one of our clinicians to come up and answer that question.

DR. WRIGHT: Tom Wright.

Currently in place in the United States are a number of

surveillance mechanisms specifically designed to look at impact on cytological rates, CIN2/3 rates, genotyping rates. You have two of the leading people on this in your Panel, and I think they could probably address this, as far as the ongoing surveillance.

DR. MAJEWSKI: Christoph Majewski again.

I should add that we actually have calculated the performance of our algorithm in the vaccinated population, and we're gladly willing to show you the data.

Dr. Behrens.

DR. BEHRENS: Catherine Behrens. It will take us a moment to get the slide up. Okay, slide up, please.

Okay. So, again, here we see the comparison of the candidate to the comparator and we -- I apologize. These are relative numbers, but I think by now you're familiar with the way the numbers go. So we can see easily that, again, the candidate compares more favorably than the comparator. But, again, there were a limited number of women that we were looking at.

DR. PORTIS: I think my question was asked, but I think it's just an extension of the other doctors, that it seems like we don't have enough data, long term, to know what's the effect in terms of vaccination because that's something that's very much just been started in the last few years. So it feels like a significant hole that we can't fill yet.

DR. BEHRENS: Keep in mind that our test, in addition to identifying HPV 16/18, also gives you a result for pooled HPV, and the recommendation is that women even who are vaccinated continue to be screened for cervical cancer. So even if HPV 16 or 18 weren't present, we would still be able to identify the 12 other genotypes. So there isn't any reason to believe that it wouldn't work in the vaccinated population for the other genotypes.

DR. PORTIS: Just an extension of that. And what about there's this figure about the percentage of HPVs that don't show up at all? I think it was 9%. I'm concerned about that 9%. Is that the number?

DR. BEHRENS: I'll give you the crude numbers because I think they're a little easier to understand. There were 274 cases of CIN3, and there were 22 that were cobas HPV negative, and out of those, 13 were both cytology and cobas HPV negative. There were nine that were cobas negative -- I'm sorry -- yeah, nine that were cobas negative and HPV negative and only six that were CIN2 or greater that were negative by all of the HPV tests. So we're talking about a very small number of cases out of a large disease pool.

DR. PORTIS: I guess that goes into my other concern, which is I know we have to look at the large public health numbers, and yet, when you're a person with cancer, you're an *n* of one.

DR. BEHRENS: Right.

DR. PORTIS: So I remain concerned about the HPV, the 9.4

that's missed. And there's mention in the data about the other cancers that aren't picked up --

DR. BEHRENS: Okay.

DR. PORTIS: -- if we don't go with co-testing.

DR. BEHRENS: Okay, can I finish? Out of the 274, the 13 that were cobas negative and cytology positive, there were 119 that were HPV positive and cytology negative. So, again, we have to keep going back to the comparison with cytology.

DR. PORTIS: There are some things that would get picked up by cytology and not by the cobas; is that correct?

DR. BEHRENS: Right. That number was -- there were 13 in the whole study, but 119 that were HPV positive and cytology negative.

DR. WAXMAN: Going back to your -- I'm sorry. Alan Waxman. Going back to your chart with the vaccinated population, I'm assuming, given the time frame that the study was done and the time frame the vaccine became available, that a large proportion of those vaccinated women were older women already exposed to HPV probably, and/or incompletely vaccinated. Is that a safe assumption?

DR. MAJEWSKI: Yes, I see nodding. That's probably the case.

DR. CAIN: I'm curious. In the indication, it includes in the indication the trial design and in a sense is a guideline, which is not usual in the indications for use. I'm curious why it was written in that way and what

interests the company has in having it being written in that way.

DR. MAJEWSKI: So I think I can hand it over to Kate Simon.

DR. SIMON: I'm not sure exactly. Could you clarify what you mean by it is written for the trial design?

DR. CAIN: So if I were going to write an indication, I might write "in accordance with the physician's assessment of screening and medical history, other risk factors, and professional guidelines in women," whatever age is agreed on. But cobas HPV Test can be used as a first-line primary cervical screening. Instead we have, it can be used -- women who test negative, this is how you treat; women who test positive, this is how you treat.

DR. SIMON: So your concern is that the indication states specific triage mechanisms?

DR. CAIN: That's correct.

DR. SIMON: Okay. The rationale for that is that the data showing that the candidate is superior to the comparator is dependent upon those triage mechanisms. So we wouldn't want to leave it open-ended to the extent that people would utilize this test in a manner that wasn't actually -- where it wouldn't actually work. So we want to make sure that they're using a triage mechanism that works. A conclusion might be that it's only safe and effective when used per its indication, meaning when used with that triage mechanism. At least that's how it was evaluated. So the indication needs to

support the data that was evaluated.

DR. CAIN: So when cytology, perhaps, turns out not to be a good triage mechanism, then this indication is no longer functional? Or when we discover vaccination affects it in a certain way it's not longer functional; is that correct?

DR. SIMON: One of the questions before the Panel -- and we haven't actually read the FDA questions yet -- was how do you expect the vaccination program could impact the performance of this device versus the comparator? Not only that, but the impact of the new screening guidelines. So there are two sort of converse -- you know, opposite forces at play here. We've extended the intervals, which could lead to increased prevalence, but we've got the vaccine, which could decrease prevalence.

So it is a moving target, but we're asking the Panel, can you think of a reason why this would change anything? Has anybody given us a reason why it would change anything? That's one of our questions to you. Not we know we don't know, but is there a reason to believe that the fundamental trend here could shift because of these factors? That is one of our questions to you. And if you could provide an actual scenario, we'd love to hear it.

DR. CALIENDO: So I think it might be helpful at this point to break because the next step we're going to do is to address the FDA questions. So let's come back at 3:30, and at that point we'll have the FDA

read the questions and then the Panel will discuss them.

Thank you.

(Off the record.)

(On the record.)

DR. CALIENDO: So now what we're going to do is focus our discussion on the FDA questions. So, Panel members, you have a copy of these questions in your folder, and remember, we're going to have a discussion amongst the Panel now; and every time you speak, please introduce yourself. And we're going to start off by having the FDA read the questions so that everybody's clear.

DR. SIMON: Kate Simon.

I'm going to read FDA's discussion questions. I just want to start by saying that Question 1 is really the primary question that FDA is seeking feedback on today. I just want to make that clear.

Question 1: Do the clinical study results support the proposed indications for use of this test? Please consider the following when discussing the proposed indications for use:

a. Is the indicated age range appropriate for the proposed indication? If not, what age range would be appropriate and why?

b. Are the tests proposed in the Candidate algorithm (cytology and simultaneous cobas HPV Test 16/18 genotyping)

acceptable for determining which high risk cobas HPV Test positive patients need immediate referral to colposcopy?

c. Please assess the benefit vs. risk in using the device for the proposed indications for use, particularly in terms of the number of tests and colposcopies performed per 10,000 patients in relation to the proportion of disease diagnosed.

Question 2: Cervical cancer screening populations are a moving target for assessing new testing methods. Recommended cervical cancer screening intervals have recently been extended for both cytology and HPV co-test screening paradigms. This study population does not have a history of screening using the newer, longer screening intervals. Disease prevalence may differ in a population that has been screened under the new intervals. Please comment on how this could affect the relative performance of the Candidate vs. the Comparator algorithm. Also, this clinical study was conducted on a cohort that included only a small proportion of vaccinated women (only 1.2% of subjects were vaccinated). Please comment on the anticipated influence of the increasing impact of the HPV vaccination program over time on the relative performance of the Candidate and Comparator algorithms (i.e., performance in a highly vaccinated population with very low disease prevalence).

Question 3: The Intended Use of the Cytology Test is identification of pre-cancerous or cancerous changes in the uterine cervical

epithelium as specified in the Bethesda System for Classifying Cervical/Vaginal Diagnoses. In addition to the cancer-related diagnostic categories, the Bethesda System includes other diagnostic categories such as infectious organisms (candida sp., Trichomonas, Herpes viral changes, atypical repair, abnormal endometrial cells, etc.). The new device is not currently designed to screen for these additional diagnostic categories. Based on your clinical expertise, what is the potential impact on patients if this additional diagnostic information is lost?

So the company has given us their perspective on this. We would like the Panel's perspective on this.

Question 4: What specific warnings and/or limitations could mitigate the risk that this test will be misused or used inappropriately for the proposed indication in patient management?

I just want to point out that we have asked the company these questions. Now we really want it from the Panel.

DR. CALIENDO: So just to give you guys some background. We have until about five o'clock or so to discuss this. These are not the specific questions that we're going to vote on, but these are the questions that the FDA wants feedback. Everybody is on this Panel for a reason; you all have expertise. So we need to hear from everybody on this Panel about these questions.

So what I thought would be helpful is, we'll just start at the top.

As was pointed out, the first question is the one that is the most significant, and so it's the one we will spend most of the time on. We'll probably spend 40-45 minutes on the first question, if we need to.

Okay, so first question. Let's open it up for comments.

DR. RAND: Ken Rand.

Can I ask for a clarification? In the questions that you just read, under 1b, you said, "Are the tests proposed in the Candidate algorithm (cytology)" and "determining which high risk HPV" tests and so on, which to me sounds like doing both. That sounds like co-testing. I thought the question was using the molecular method as primary screening as opposed to co-testing.

DR. CALIENDO: I think that's referring to the triage, right?

DR. SIMON: It's referring to -- for the triage. So you've already got -- you've got the positive cobas HPV test result, and it automatically gives the 16/18 at the same time.

DR. CALIENDO: Go ahead, Alan.

DR. WAXMAN: Alan Waxman.

And I'll just jump in on one of the points, at least.

Indicated age range: There are two aspects of this. The American Cancer Society, ASCCP, ASCP -- all the A-S-C-and-P's -- got together a couple of years ago and hashed out age ranges for screening. And the consensus of opinion was that age 21 was a good time to start screening, not

age 25 and not age 30. It was also that age 30 was a good time to do co-testing.

The Sponsor has given us some very nice evidence to the effect that there may actually be some good value in using the HPV test starting at age 25. I'm concerned that the results of what we come up with may leave the clinician with the thought that well, now I don't need to start testing until age 25. And it may very well be that we don't need to start screening American women for cervical cancer until age 25, but I don't believe that this is the process by which that should be decided.

And then if we're left with a consensus that we're going to start screening at age 21, one of the things that the groups coming together to suggest follow-up algorithms for this will need to decide is, what do we tell the American clinician? Start screening with cytology alone at age 21? Do it every three years, age 21, 23? And then at 26 you can go to cobas or you can continue as such? But I think that's one of the factors we will need to keep in mind from the standpoint of ages appropriate for the indication.

DR. CALIENDO: Other comments on aging?

Not aging, in general.

(Laughter.)

DR. CALIENDO: So go ahead.

DR. MASSAD: So to me, the question in (a) is more, is 25 to 29 inappropriate? I think that's what the Panel has been reckoning with. I have

a gut sense that many of the women in that age range with CIN2 and probably some in the CIN3 group will have their disease regress without treatment and will not benefit from screening. I can't quantify that. Certainly it would be unethical to ask the question about CIN3. To me, the proposed indication is not inappropriate. I am concerned about it but can't say that it's clearly incorrect.

DR. CALIENDO: Can I just ask the concern?

DR. MASSAD: It's safety.

So just for the other Panel members, in meetings that have discussed safety of screening, the concern has been that it's hard to define harms from screening for cervical cancer. I think Dr. Cain had asked earlier about how to translate colposcopies into numbers of LEEPs or treatments. We really can't do that. We can't go so far downstream as to look at number of pre-term deliveries that result from over-screening.

But looking at number of colposcopies gives us a relative measure of harm from screening because a certain number or proportion of those will be translated into those harms downstream from over-diagnosis and over-treatment.

By the way, I didn't mention I'm Stewart Massad, for the transcriptionist.

So if we're diagnosing HPV disease, it's destined to regress in that youngest group. There will be a proportion of women who are harmed.

We heard today from women who might have avoided morbidity from cervical cancers being missed by HPV testing. We will never hear from women who were harmed by screening because most of them will be persuaded that they actually benefited. It's hard to put a number on that.

My remarks are deliberately inchoate because the data are just not very strong for how to quantify harms, but we know that they're greater for the youngest age group. Clearly, I think it's inappropriate to be applying this test to women 21 to 24.

DR. BURK: So in thinking more about the age differences and some of these other factors, I think the thing that's weighing in -- and Stewart, I'm agreeing with you -- is the negative predictive value. And I think that, from the data that we've seen, the negative predictive value improves.

Certainly, if you did co-testing, I can't say -- and I haven't seen that it's statistically better, but certainly the negative predictive value of the HPV test, even in this younger group of women, most of them will be negative; they won't go to cytology, and as vaccine actually occurs, there will be less 16 and 18, so less will be referred to colposcopy. So, in fact, it might even be preferable, as we move in and we really focus on the negative predictive value as being at least one metric to use to think about age.

DR. BIRDSONG: George Birdsong.

I just want to point out what I think is implicit in Dr. Massad's comments -- but correct me if I'm wrong -- is that we, as pathologists, really

can't -- abnormal Paps or abnormal biopsy, while we recognize that many of those left alone will regress, we can't tell which ones they are. And it would be interesting to actually -- you know, when you hear from the public -- I mean, we're a little bit removed, working in the lab. But I suspect if there was a way for us to ask women now -- you know, nothing is perfect here; if we are too aggressive here, we may do something that causes future obstetric morbidity on the one hand or you may get cancer on the other hand.

I suspect that a significant portion of the public would opt to avoid cancer, and it depends very much on how you present that to them, obviously -- you know, which way a patient might decide to go there. But obstetric morbidity is not a good thing, but cancer is probably worse.

DR. CALIENDO: This is Angie Caliendo.

So, George, if I may ask what you're thinking on the 25 versus 29 limit? And I'm going to be asking everybody this, so --

DR. BIRDSONG: That's a tough question. I don't know. I'm agreeing with Dr. Massad. I don't think we have great data to answer that question, but in speaking of patient safety, I think we just need to be mindful of those two alternatives and what is the lesser of the two evils. I guess I might slightly favor being more aggressive while acknowledging there is a very strong argument to be more conservative.

How's that for a non-answer?

(Laughter.)

DR. CAIN: So this is Joanna Cain.

I'm still looking at this, 704 colposcopies versus 480, which is our only marker for the potential for safety or harm. And I think, being an oncologist, I of course think cancer is more important. But having listened to patients over the years, I can't discount how traumatic and how significant loss of pregnancy is and that it's related to the choices we make based on our screening methodologies. And that's the safety issue at hand, and we have no follow-up information. We really don't have the answers that say how big a risk it is, which is why we're all fumbling to answer this question. But I think that's the way that's hard to do because the data isn't there in this study to answer that question.

DR. CALIENDO: So this is Angie Caliendo.

Can I ask you a question, because I actually don't do obstetrics or gynecology? When does someone go to LEEP, at CIN3 or -- you know, does colposcopy correlate totally with risk, I guess in my brain is what I'm trying to understand.

DR. CAIN: So therein lies the problem with the safety analysis. You would hope people aren't doing LEEPs for CIN2. They may do LEEPs, mostly do LEEPs, for CIN3 or to answer a question. But this is an idealized study, right? It isn't applied in the general population where somebody may be doing a colposcopy, they're just not sure -- and boy, the LEEP is right there.

So we don't know, in the general population, how commonly LEEP would be used as a solution to a quandary.

DR. WAXMAN: I would throw in an additional caveat. LEEPs are done commonly -- routinely for CIN3, commonly for CIN2, and in some places still for CIN1, which is not recommended. The caveat that I would throw in is to be careful with equating colposcopy with LEEP and LEEP with prematurity. The data on premature births with LEEP is still very conflicting. A lot more of the European data is showing an increase in prematurity than the U.S. data, so it's one of those nebulous statistics that we keep in the back of our mind. But it's not a -- "if LEEP, then pre-maturity" -- kind of thing. Number-needed-to-treat goes anywhere from 19, I think, to 400 depending on the study.

DR. MASSAD: So the ASCCP guideline, which I think is the national standard, says all CIN3 should be treated, all AIS should be treated. CIN2 is treated unless the patient meets certain exceptions. CIN1 may be treated if it's persistent for two years or longer.

DR. CALIENDO: Okay. So we need to get back to the age limit, and so this side of the table has been rather quiet.

So if people -- go ahead, Paula.

DR. HILLARD: Paula Hillard.

So it has been alluded to, in terms of potential morbidities related to lesions that will regress -- and the pre-maturity has been

addressed, as well. And it certainly is difficult to look at in terms of the science, but if you ask women about other potential morbidities, I hear a lot of anxiety about having to have a colposcopy, about potentially having cancer, of course, but the need for a colposcopy and biopsy related to that. So hard to measure, but it's there.

So one of the things that concerns me is looking at overall HPV positivity in the 25- to 29-year old age group, and so not just 16 and 18 positivity but the other high-risk types, as well. And as I look at the table on page 13 in our book, that was 21%. So I will be faced with 21%, a fifth of my 25- to 29-year old patients who will be anxious about potentially having cancer.

Now, I'm hearing the guidelines, and I'm participating in the discussions, and I know what the recommendations are going to be, but I'm concerned about where this will go in general use. I'm concerned that potentially all of those women with the other high-risk positivities will not go to having Pap next, but those patients will go to colposcopy. And so that will magnify the potential morbidities of colposcopy.

So that's not what is proposed here, but what control does the FDA have over what happens in reality and practice once this is out there? I'm not wanting to miss the CIN3, either, in those 25- to 29-year olds, but it's an issue that I think needs to be on the table.

DR. CALIENDO: Yes.

DR. NOLLER: Ken Noller.

I was going to make the same comment, Paula.

Twenty percent of these women are going to have colposcopy in the 25- to 29-year-old age group. I've done enough with the practice division of ACOG, watching how people practice. If you're high-risk HPV positive, they're going to get colposcopy. That doesn't necessarily mean, though, that it's bad. It's what you do with the colposcopy, and that's where, I think, we have a lot to teach our practitioners.

I was somewhat biased against dropping the age to 25 before I came here, looking through this, because all the other guidelines are 30. I thought we're just going to confuse people more. If the data look substantially the same, why not leave it at 30; let's just change our recommendation. But I find the data that has been presented today somewhat compelling to drop it to 25. I'm going to listen to the rest of the discussion, but if I had to vote right at this minute, I'd probably vote to drop it.

DR. SIMON: Kate Simon.

I just want to point to the slide that's being displayed and that you all have in front of you. Just a reminder that in this age group it would be actually, by the candidate algorithm, 10.58% that's referred to colposcopy versus 7.21% with the additional comparator. And the comparator of 9.8% admittedly, that's with the 2006 guideline where all ASC-US are going straight

to colpo, so that's a little elevated. But we just want to make sure -- you know, someone said 20%, but it's 10.

DR. NOLLER: This is for 16/18. We're saying that if you include all of the high-risk HPVs, it's 20%.

DR. SIMON: It's not just 16/18, it's the candidate algorithm. It includes every one that is 16/18 positive and high-risk HPV 12 other positive that had a positive cytology result.

DR. CALIENDO: Go ahead, Paula.

DR. HILLARD: Paula Hillard.

I'm looking at Table 13 in our book. It's Table 1 on page 13, sorry.

DR. SIMON: Table 1 on page 13 tells you the percent of women that are just simply high-risk HPV positive, so -- right. But they don't all go to colposcopy before the candidate algorithm.

DR. HILLARD: The point is that in practice, many of those women will be -- so potentially. The concern is that those women who are HPV positive will not follow the algorithm, will not then go to having Pap and cytology.

DR. SIMON: Yes. We just want to make it clear because someone stated that in that age group, 20% would go. And we just want to make clear the distinction of the fears of off-label use here. That's fear of off-label use that we're talking about, a legitimate discussion point. I just wanted

to be clear.

DR. NOLLER: We are just making the point, it is used. It's not the proposed language. But in real life, 20% will have colposcopy.

DR. PORTIS: From the patient perspective, I just want to echo --

DR. CALIENDO: Natalie.

DR. PORTIS: Oh, Natalie Portis -- what Dr. Hillard is saying about what you all may decide and vote on today versus what happens. And once patients have the information, what kind of things they're even pushing for and encouraged to do, and we've seen that happen in other cancers with over-treatment. And then people's anxiety gets stirred up, and they want to do more extreme measures maybe than the guidelines say, but it then happens all the time.

DR. BURK: So I think this relates to physician practice. And so one of my closest friends is an endocrinologist; whenever he sent a patient to a gastroenterologist, they always got scoped just to be sure, you know, plus the financial compensation just to be sure it was extensive. So I think everything -- it's absolutely correct, and it's going to have to be the insurance companies. They're going to have to come in and say you have to follow policy because it's difficult to regulate doctors.

You know, it's one of the problems in getting the best care and the best way to protect women in the country and to decrease morbidity

through, you know, the skearing (ph.) and these other procedures, but I think, from the data we've seen, again, the negative predictive value, we'll be doing less cytologies on that group. And so it's a tradeoff and the data has been pretty strong. But we need -- you know, it's a problem about dealing with doctors.

DR. MASSAD: So this could be something --

DR. CALIENDO: Introduce yourself.

DR. MASSAD: Sorry. Stewart Massad.

Under Question No. 4, that the FDA may tell clinicians that colposcopy is not indicated for women with HPV-positive other 12 types positive, without a triage test.

DR. WAXMAN: Alan Waxman.

I just have a quick procedural question.

When we are asked to vote on this, are we asked to vote on it as is, or can we amend it? Could we, for instance, vote on it except to start at age 30 or age 40 or --

DR. CALIENDO: So we won't be voting on these questions. We'll be voting on different ones.

DR. WAXMAN: Yes.

DR. CALIENDO: But I would ask the FDA, can we give contingencies, or these are up-and-down votes?

DR. SIMON: You know, I would actually -- Sara. Captain --

sorry. Could you address that question, because you know the procedure?

I know that you can, in fact, propose modifications. I'm just not sure if you vote on proposed contingencies on the vote or if you propose an alternate one you want to vote on.

LCDR ANDERSON: Hi. They're voting as is.

DR. SIMON: But can you clarify --

DR. CALIENDO: That's the purpose of this discussion, as I understand it, is to put things into a context, and we will make recommendations to Dr. Hojvat at the end of each of these questions, to say this is the general take by the Panel, and then they can take that back and put it in the context of the results of our questions. Is that correct?

DR. HOJVAT: Yes, that is correct.

DR. BIRDSONG: Question. I hope a quick question; it's for the OBs on the Panel.

I don't know. We've talked about the increased risk of prematurity with LEEPs. Is there a number from the OB literature on what that number is? You know, 10%, 25%?

DR. MASSAD: I can try to answer that. It varies from zero to twofold, which -- this is Stewart Massad.

If the background prematurity risk is 5% to 10%, it goes up to maybe 10% or 15%. Most of those will be in the 34- to 36-week range, which does well. But there is an increase reported in the youngest prematurity

group in the 24 to 26 range. There is some suggestion that LEEPs done in the United States are not done with wires that are as big as the ones used in the studies that have shown an impact. And many U.S. studies -- well, some U.S. studies have not shown an impact on prematurity.

DR. BIRDSONG: George Birdsong.

Prior to the meeting, I attempted to do a literature search on that, and I quickly realized it was more complicated than a non-OB was going to figure out in the time available.

DR. MASSAD: Stewart Massad again.

The problem is that women with abnormal cytology are at increased risk for prematurity, and getting that confounder out of the question is extremely difficult.

DR. CALIENDO: Mona and Beth, your thoughts.

DR. SARAIYA: Well, I wanted to mention that I'm a little confused about the 25 to 29 because of many of the reasons that were stated. Mostly, some of the harms -- and as I mentioned, in many of the trials, first of all, we don't have an organized grading program. Being diagnosed with HPV-positive infections is stigmatizing in the United States, and we don't know what the follow-up or the compliance rate would be in this group. So that's one concern.

The other concern is that when you look at those women that are under surveillance, I mean, the harm is colposcopies for those women

that don't need it, but then there's also just long-term surveillance. And there are a significant number of women 25- to 29-year-old, 10.6% compared to 4.9%, that will be normal cytology and be positive for the other high-risk 12 types that are probably at low risk, long-term risk. And that's a new group that you're introducing this grading to -- the 25 to 29 -- because they haven't had the HPV test before. So something that I'm grappling with.

And then, again, with guidelines and adherence, everyone's doing different things in terms of following HPV-positive tests, even though there might be guidance set. And it is adding one more strategy -- you know, the United States has barely gotten the second strategy in place in practicing that. But there is some compelling evidence, as well, in terms of the increase in sensitivity and comparable specificity.

DR. UNGER: This is Beth Unger.

And I came to the meeting somewhat skeptical why age 25 was selected just because it was a new introduction to the guideline. But I've been persuaded by the data that was shown here that there is -- with the evidence that we have a reasonable approach. And what people are going to do with the recommendations, and this is really in-ponderable, and I think we have to stick to the science and make the best recommendations we can on the science and then try to educate people to use it appropriately.

And it would be a shame to not let the best technology be available because we are afraid people are going to misuse it. And so I do

think one of the biggest problems in shifting technologies is long-term follow-up. We've got a lot of holes in this. The algorithm is good up to the first time, but just like Mona said, we're going to have a group of women with the high-risk positive not 16/18 that are cytology negative; what do we do with those long-term? We don't have any data on that. And that's going to be a real confusion for the field, but I don't think that that should deter us from trying to sort it out.

DR. CALIENDO: I don't have a feel for how you weigh the concern versus the data on the 25 to 29, so is it enough to say I don't think we should go that low, or we should go that low but these are things that people need to understand.

DR. CAIN: So my personal view is that it's okay to go that low for screening, but I think we need to keep an eagle eye on the long-term consequences of having done that, and also significant attention to education and training for clinicians. I think without that, there is a potential of harm.

DR. WAXMAN: Alan Waxman.

I think we also need to recognize that if we approve that at the 25 to 29 age group. Right now, I like the whole package, except I'm not real happy with that segment of it. One thing we need to keep in the back of our mind is that we've got nice data here, as far as it goes, and people are talking long term. I'm thinking short term, the next step. There's no data to inform. I mean, a 26-year old comes in and she is positive for one of the 12 other

high-risk types and her Pap is negative, we don't have any data to tell us what the best next step for that is. We're going to extrapolate some from an older age group, but we don't know.

DR. MASSAD: Two points.

One is that I think we've agreed that there is effectiveness, but the question is safety in this group. We can't discuss interval, but interval will impact safety if you screen. Dr. Burk probably knows the data better, but if you have a 21% -- like we've heard of -- high-risk HPV in this age group at a single screen, if you test twice in that age range, then you'll probably hit about a third of women will be positive. If you test them annually for five years, you may hit 50% positivity. So screening interval will play into safety.

And then this is unrelated, but related to the question. I do not see evidence that would allow us to give an upper age limit. We've talked about lower age limits, but I don't see that we can put an upper age limit on this.

And this has been Stewart Massad. I didn't identify myself.

DR. CALIENDO: Okay, go ahead.

DR. BURK: Robbie Burk.

So clearly HPV is transient if we are able to look at the same type. The issue is in the mixed probe; they're not going to be able to distinguish 68. So from our experience, it will clearly drop, but it's not as powerful as having specific information. I mean, that could also get to some

of the types that are included that are very low risk for cervical cancer. And by IARC -- they're not even in the IARC list, but I guess we have the package, as is. And clearly I think the issue speaks for itself.

In the comparator, you have the cytology, and that those would drive the women to, I guess, further examination such as colposcopy. And the candidate is a little bit higher. But I would imagine that in the 12 types that you're testing for, it's unlikely to be persistent, and their cytology is probably likely to be not that significant. We know, from Portland, where they did a single test, the risk of CIN3 -- if you exclude HPV 16/18, was extremely low over a long period of time.

Now, that was a mixed group. That was not just the age group of 25 to 29, but that was a low group. And we know, from other studies, that HPV risks, after acquisition, is similar at different age groups. So we could extrapolate that. In fact, these other types are not going to be nearly as significant as the 16 and 18 that are really kind of our big problem.

DR. WAXMAN: Alan Waxman.

They are not individually as significant. You're in an age range that has the highest prevalence of HPV positivity, of high-risk HPV positivity. It's also an age group that is more likely than older women to clear one HPV and acquire another one in, perhaps, the year's interval between testing, which is going to bias the management towards increased colposcopies. It's problematic.

DR. CALIENDO: I'm sorry, can we hear from Glen and Cherie?

MR. FREIBERG: It's hard for an industry rep to get involved in a medical discussion because you're talking about different practices. As far as the safety goes, my interpretation of what's been presented supports the application. Now, what a doctor does is an entirely different subject than what's put in the labeling and promoted. And I think that the Panel is going to have to separate that out and come back to the point that several people have made in regard to education if and after the approval. But that practice guideline, what the individual doctors do, the intervals, it's really independent of the safety of the data that we've been presented, in my opinion.

DR. SCOTT: Cherise Scott, Consumer Rep.

I just feel like the data -- there's not enough data for me to feel comfortable with extending it for the 25 to 29 age group. I just feel like, I don't know, with that balance of safety and so forth, I just don't feel like I have enough data around that to feel comfortable with that.

DR. BLUMENSTEIN: Well, I think it's really nice that we have data where we have to think about this. But on the other hand, I'd like context to be able to comment on this question, since I don't treat these patients. And the doctor knows best.

DR. CALIENDO: Lizzie, any thoughts?

DR. HARRELL: Lizzie Harrell.

I look at the data, and I'm thinking if you look at the data alone, maybe I'd feel comfortable starting the testing at age 25. However -- and the question I asked earlier today, how are the professional societies and physicians going to use this recommendation, then I'm not quite sure if I'm really comfortable with it. So I'm still questionable.

DR. NOLLER: Just let me add that right now, doctors are doing all sorts of things, not necessarily what the guidelines are, right? We know they're LEEPing people that have trichomoniasis, for all I know.

(Laughter.)

DR. NOLLER: So I agree, we have to look at the data and make a decision on what science we have, and if that science supports something, I think we should approve it. On the other hand, if we think more science is needed, we're unsure, then we shouldn't. But we don't know what doctors are going to do. We can try to educate them.

DR. HANSON: I guess one thing I keep coming back to was the cervical cancer incidence per 100,000 patients that was presented by the Sponsor, and you see that the curve has taken off right around the time women turn 25. And so we now have an opportunity, I think, with a very sensitive and specific test, to potentially identify women earlier. And to me, that's compelling.

Granted, there are, I think, only 2,000 patients in this age range in the clinical trial and the observation or the fact that we know that some of

these women may regress on their own and not necessarily need treatment. And in this age range we're probably going to be sending more women to colposcopy based on this assay. But I guess what I'm hearing from the obstetricians on the Panel, and the gynecologists, is although colposcopy is invasive and can be anxiety provoking, for the majority it's really very safe. So I think I'm leaning more towards earlier screening to detect and prevent cancer in younger women.

DR. CALIENDO: Ken.

DR. RAND: Ken Rand.

My inclination is to lower the limit or the age of screening to 25, and I think just based, sort of, straight on the data. And obviously, not being in the field, I don't have the same concerns or regards -- or experience, I guess, is a better word -- for unintended consequences. But we're going to have unintended consequences no matter what we do, and my inclination is that we probably will pick up more cancers. And in the end, this is likely to be beneficial overall.

DR. CALIENDO: Angie Caliendo.

What other thoughts do people have? Comments?

Go ahead, Alan.

DR. WAXMAN: I'll throw out one last thought on this. And that is while I remain somewhat skeptical for all the reasons that I discussed earlier, our charge is to compare it to the comparator, and the comparator is

cytology, and the data looks very good. So given that charge, I'm inclined right now to vote for it.

DR. BURK: Robbie Burk.

I would like to agree with that strongly, that we can think of it in a vacuum, it's almost "versus Pap smear" because we're not going to ignore the women 25 to 29 in screening, so they're going to get some screening. And this really gives us the opportunity to use what we've learned in science over the last two decades and improve it. And hopefully there will be further improvements to the technology to molecular diagnoses. But certainly, as the comparator, I agree with exactly what you said, and I would support the 25 years at the point.

DR. SIMON: Kate Simon.

Could I add something?

I just want to emphasize to the Panel that it would be very helpful, when you make your vote, to consider that when FDA is considering the Panel's recommendations, it's very helpful to know that the recommendation was made based on the data -- you know, in support of the device as it's actually intended to be used and not as it's feared it might be used. So it's helpful to know that you made your decision based on the device -- you know, in accordance with its intended use. It just helps. It makes it easier to consider your recommendation if we know you're doing that.

DR. CALIENDO: So my summary of this discussion is as follows, and it's open for correction. I think the majority of people, but not everyone, supports the recommendation of 25 to 29, and that if you look at the data, the data are compelling. The concern is of how it will be used in clinical practice. So it's more -- as Kate said, its off-label use of it. And there's a very strong need for there to be education programs out there and to probably modify guidelines that exist so that everything can be done to have these tests used as directed.

DR. SARAIYA: Can I make clarification on what Dr. Massad said? He said there is no upper age limit, but my understanding is that there were very few women above 65 that were actually examined in this population, so I'd like to understand because this could be used in women 90 and older.

DR. CALIENDO: I mean, my comment about that is if you look at every guideline that passed before our eyes, nobody's screening women over 65 for any reason unless they have -- you know, there's an exception. But as I read those guidelines, as long as they've had several screenings that are negative in the last decade, they're done. So I don't see this going beyond 65, but --

DR. SARAIYA: I guess there's an indication, and there's going to be a while before there are guidelines. And even though there are guidelines in place for not screening women over 65, it does take place just as screening

women with a cervix.

DR. CALIENDO: Stewart, do you want --

DR. MASSAD: I was just going to clarify a point you made. You said the data are compelling. I would argue that the data on effectiveness are compelling; the data on safety are less compelling. Personally, I don't find them sufficient to vote against a 25-year-old group, but I would find high frequency screening in combination with a 25-year-old start to be problematic.

DR. CALIENDO: Okay, any other comments before we move on to 2b [sic]?

(No response.)

DR. CALIENDO: Great, thanks.

Sally, do you have any questions that need clarification?

DR. HOJVAT: No, I was just intrigued with the need for more data, and so how do you get that data? Usually, what happens is, is a new test goes out. We've done the safety and effectiveness part of it, show the data, and then it goes out, and then papers are published on it when it's out in use. You can either do that or you can ask a company to do a post-marketing study, but very often it's once something new is out there, then the papers come in, and it's really the clinical community that then judges that test.

In fact, I've heard clinicians say that's how we like to do it, you

know, you go through the safety and effectiveness; we'll determine whether this actually is useful in a clinical sense. So I just wanted to make that comment that, you know, how do you get more data than you have already?

DR. KONDRATOVICH: Marina Kondratovich.

I would like emphasize that in your package is there information about number of patient. It was more than six and half thousand, so this sample size for this statistical analysis for performance. So it was in study more than 40,000 and around six and half thousand were in this age range. So this was the amount of the data for this conclusions for on the screen.

DR. CALIENDO: All right, so let's move on to 1b, which is "Are the tests proposed in the Candidate algorithm acceptable for determining which high risk cobas" tests -- who tests positive and who needs them, referral to colposcopy.

So how do we feel about using cytology and 16/18 genotyping as the triage?

DR. WAXMAN: I find them very consistent with the ASCCP guidelines. They just reverse the order a little bit. ASCCP says that if the Pap test is negative for intraepithelial lesion malignancy and the genotyping is 16/18, you go to colposcopy. Well, if you're going to colposcopy, you don't need the Pap test.

The guidelines say that if the test is positive for high-risk 12

other types and the Pap test is abnormal, you go to colposcopy. Well, here you've got positive for the other types, we'll do the Pap test and see what it shows. So I find it cleverly done and very consistent.

DR. MASSAD: Stewart Massad.

In the interest of time, I would say 1b, yes.

(Laughter.)

DR. CALIENDO: Does anyone have a different opinion on 1b? Not to stifle discussion.

(No response.)

DR. CALIENDO: Okay, it looks like everybody is happy with 1b.

Okay, so now 1c is "Please assess the benefit vs. risk in using the device for the proposed indications for use, particularly in terms of the number of tests and colposcopies performed per 10,000 patients in relation to the proportion of disease diagnosed."

DR. NOLLER: I would suggest we've already had that discussion, really. I would have nothing to add beyond what we've already said.

DR. CALIENDO: Does anybody want to discuss, when we have our up/down vote, are you comfortable having the up/down vote as the indication is written, or is there any additional information that you want to convey to the FDA that we haven't already -- yes?

DR. PORTIS: I'm not sure if this is the right -- Natalie Portis --

moment, but I want to keep being a strong voice for co-testing and not eliminating that.

DR. CALIENDO: And, you know, my take on the day has been that this would be in addition to co-testing, but it wouldn't be an elimination of co-testing. And please, is that other people's assessment of what we've been discussing?

DR. SIMON: Kate Simon.

That is correct.

DR. CALIENDO: Okay. So I think that's an important point.

Anything else that you feel -- go ahead, Glen.

MR. FREIBERG: Glen Freiberg.

Since you asked for affiliated comments, I just wanted to reiterate a suggestion to the FDA to ask the Sponsor to include a table for the rest of the data from the 21 to 25 group so that the clinicians have all of the information in one place.

DR. SIMON: Kate Simon.

We don't normally include data in a package insert that doesn't support the proposed indication. It can imply off-label use, so we don't do that.

DR. CALIENDO: So related, can you separate -- since most of the discussion today has been about the cutoff of the age, can you separate the 25 to 29 versus the greater than 30?

DR. SIMON: Yes, we can do that.

DR. CALIENDO: Okay. Is that something that we would like to see done?

UNIDENTIFIED SPEAKERS: Yes.

DR. CALIENDO: Okay.

Okay, any other comments? This is your big opportunity.

DR. UNGER: Since you put up the slide that shows the candidate unblinded versus the candidate blinded, I was kind of struck by the difference in performance with that. Would that be included in the packet, you know, as part of the data?

DR. SIMON: Yes, it would.

DR. KONDRATOVICH: Because it's based on additional study and candidate unblinded is more -- we think it's more realistic performance, what you can see when HPV status is available for cytologists doing cytology. But the first candidate is what you see in ATHENA study when without HPV status was done.

DR. CALIENDO: Okay, can we pop the Question No. 2 back up, because it's long and I would -- oh.

Sally, do you have any other questions about 1b and 1c?

DR. HOJVAT: Sally Hojvat.

No, not at this point.

DR. CALIENDO: So if we can pop up Question 2, because it's

rather long. And this is the one that's getting at the vaccine.

So we will have all these discussion questions, there are five of them -- four of them. And then we will go back and vote on the three specific voting questions.

Okay, any comments? What's the discussion on Question No. 2?

DR. MASSAD: Stewart Massad.

I can start.

I think Dr. Wright -- with the Sponsor -- summarized this, that the prevalence of disease should decrease. We have not seen any data that suggests that sensitivity or specificity will change or that there will be a differential change in positive or negative predictive value relative to other screening systems. So screening overall, regardless of the modality, will be less accurate because there just won't be as much disease to find. But I haven't seen data that that will differentially affect an HPV screen.

DR. UNGER: I basically agree, although I do think that it will have a bigger effect on cytology than on HPV, which is kind of straightforward detecting, because there are a lot of other changes that influence the way the cells look besides neoplastic progression. As vaccination really starts taking place in primary prevention, it works better; the screening test will be less effective. Not unnecessary, but we're going to end up with less disease to find.

DR. WAXMAN: Alan Waxman.

One of the early concerns when the vaccine was being rolled out was that by eliminating 16 and 18, other HPV types would then move into that niche and increase. And to my knowledge, we have not seen any of that happening. When we have a more fully vaccinated population, the cobas 16/18 test will show up very few positives. The 12 others should still be valid, and I don't know of any data to suggest that non-HPV cancers will suddenly start popping up, so I think it should work.

DR. CALIENDO: So interesting comment about the other types. It's probably too early. When you think of the percent of people that are vaccinated and how long the vaccine is out -- so it will be interesting to see what happens over the next couple decades.

Yes, Robbie.

And then go ahead, Mona.

DR. BURK: Robbie Burk.

So Australia has been vaccinating a long time. Is anybody on the Panel familiar with some of the screen -- not -- their vaccine does them good. I think they've shown a reduction of CIN3; certainly warts, they have. But does anyone know how their screening results have been? Because they've vaccinated a very high proportion of the population. That might help guide us.

DR. SARAIYA: I can't fully comment on it, but there are two

studies that have come out. One came out that was ecological, that looked at pre-vaccine and post-vaccination and showed a decrease in CIN3. This latest one had vaccine status, but I think in the vaccine circles, they're questioning the data itself just because the vaccination took place. They didn't see a quick dose response, et cetera, and the vaccination took place among young women that might have already been exposed to the HPV, so it wasn't clear-cut.

But I believe that there's even a stronger study that just came out in Denmark this last week or so that actually showed some decrease in CIN2 and CIN3. And, obviously, you've recorded the genital warts reduction.

My comment was about making clear that what this particular study could and couldn't do because the vaccination was occurring among mostly women that were already exposed to the virus, and the rest is, in my opinion, more of a theoretical discussion because we have no data to support this. But I would just add that we have to make sure that it's a fully vaccinated population and the vaccine was given prior to exposure, so I'm not sure what the discussion would lend itself to right now because it's quite theoretical.

DR. CALIENDO: Nothing to add?

(No response.)

DR. CALIENDO: Okay.

So Sally, I think, for Question -- I'm sorry.

Kate, did you want to say something?

DR. SIMON: I just wanted to add that we do realize, of course, the question is completely theoretical. But we did want to ask you just in the context to be sure that nobody did have a scenario in their mind in which there could be possible effect of the vaccine or the new screening guidelines that would potentially change the relative performance of the candidate versus the comparator. That's the main reason we asked it. So just, if anyone has thoughts on that.

DR. SARAIYA: I think we addressed the vaccine issue, but the other one that you raised is just as important, right, the interval issue? Yeah. I don't know if you wanted discussion on that.

DR. CALIENDO: I'm sorry, Mona. What are you saying?

DR. SARAIYA: Well, there are two questions here, right? The one would be the lengthening of the screening intervals and the new guidelines with going to every three years or every five years, because the current study population was pretty much operating on cytology-based screening and maybe routine screening on an annual basis versus lengthening it, so you would hypothetically imagine a higher prevalence.

DR. BIRDSONG: George Birdsong.

That's kind of what I was going to say, that the increased intervals might have more of an effect -- I think Dr. Unger said that, too -- on cytology than the HPV test, but that's still speculation.

DR. RAND: Ken Rand.

I'm not sure about the statistics on this, but it seems to me that if vaccination lowers the incidence of HPV 16/18 -- so you sort of take those out of the equation. I'm not sure that the biological test performance changes, but what does change is -- if you remove them because your prevalence is lower, then your percentage of false positives goes up. But I'm not sure it affects the absolute numbers of women who would be so affected.

DR. CALIENDO: Actually, I think, Sally, that's a very good summary, what Ken just said. You know, the prevalence is going to go down with vaccination; the test performance analytically may not change -- or even clinically -- but the value of the test may change only because the prevalence is down.

DR. HOJVAT: Yes, Sally Hojvat.

I mean, this kind of thing happens all the time. You know, there may be a different population; that's obviously what this is. Somebody may have a different -- like the flu tests, they keep changing. So we have to be very flexible. If it does appear that there's a change in the performance over time, then the company has the opportunity to present data and send in a supplement to the PMA, and we will change some of the things in the package inserts.

I'm being a little bit -- because we don't know what it is. If it's something really dramatic, then, of course, you could change the intended

use. But if it's something identifying a different population, very often that would be a new table of information in the package insert based on study data or literature.

DR. CALIENDO: And so this gets to the question that came up earlier in the discussion, which is, can you change? You know, if we approve this, are we approving it forever? And I think that's kind of what Sally is saying, is that data changes, new data comes in, and things are reassessed.

Go ahead, Stewart.

DR. MASSAD: Mona had mentioned the Danish study that was published last month in *JNCI* -- this is Stewart Massad -- that shows a 50% or a little bit more than 50% reduction in CIN2+ in women who were vaccinated before age 20, but not in older women.

DR. CALIENDO: I'm sorry, 15 or 50?

DR. MASSAD: Five-zero.

DR. CALIENDO: Five-zero.

DR. SARAIYA: But luckily -- I mean, unluckily in the United States, we don't have such high coverage and the same kind of vaccination issue.

DR. CALIENDO: Okay, any other comments on 2?

(No response.)

DR. CALIENDO: All right. So on to 3 we go.

DR. WAXMAN: Three is an interesting question.

Are you going to read it first or --

DR. CALIENDO: No.

DR. WAXMAN: Just comments?

Three is an interesting question because really cytologists give us all that information. But as a clinician, most of us don't pay a whole lot of attention to it.

I know, I know.

You know, sometimes we diagnose candida, trichomonas, rarely herpes, but there are much better ways of diagnosing that. The Pap test is not intended as a screening test for those things. Repair, that's cool. Abnormal endometrial cells, very infrequent finding but can be useful. But I don't think that the loss of the Pap test is going to make a huge clinical impact from that standpoint.

DR. CALIENDO: Angie Caliendo.

I would say, from my perspective from infectious diseases, if this is how you're diagnosing trich and herpes and other infectious diseases, there are much better ways of doing that than the Pap smear. I don't see that as a loss at all.

Go ahead.

DR. MASSAD: Stewart Massad.

I would concur with what Dr. Waxman said and would point out that there is no known effective screening test for endometrial cancer, which

is what abnormal endometrial cells are for. We don't do Pap tests to screen for endometrial cancer.

DR. CALIENDO: Kim, do you have a comment as another microbiologist in the room?

(No audible response.)

DR. CALIENDO: Anybody else?

(No response.)

DR. CALIENDO: So any comment, Paula or Ken, on how you use the results of --

DR. NOLLER: Ken Noller.

I agree totally. You ignore it. I suppose it's possible, in pregnancy, you might think about it, but we're not doing many Pap smears in pregnancy anymore. So I think it's sort of useless information. If a person is asymptomatic that has changes suggestive of BV, you ignore it, so --

DR. CALIENDO: Okay. So, Sally, the consensus appears to be that it is not a problem to lose that information.

DR. HOJVAT: Okay.

DR. CALIENDO: Okay, our last question. Number 4.

This is something we probably should think through and give the FDA some guidance. The one thing that's already come up is to put in the package insert that colposcopy would not be indicated for people that have high-risk HPV that is non-16/18, that the triage algorithm is out there.

Anything else people want to discuss?

DR. BIRDSONG: George Birdsong.

In a nutshell, everything in the CETC statement. It's one of the public -- the CETC statements that had to do --

DR. CALIENDO: Can we find that so we can all go through that and make sure -- the one that has CAP on the front.

DR. UNGER: This is Beth Unger.

While everybody is looking, I mean, I do think we need to specify the collection media that is was verified in and not -- it's not approved for other collection media and other collection devices.

DR. SARAIYA: So that would go for cell collection, and I think there was -- okay, great. And then the issue about hysterectomy or where it was raised would be a good point.

DR. BURK: Robbie Burk.

So at some point it would be nice to put in what the World Health Organization defined as oncogenic HPV types and that some of the types in the current test are not in the highest list and they're rarely associated with cervical cancer.

The other thing that I would like to say is that in some populations HPV 45, as 18, is associated with adenocarcinoma, which is poorly detected by cervical screening. So population bases could make a difference. In 45, they don't pull out 45 and combine it with 18 but kind of,

as a papillomavirus person, knowing that 45 can also be associated with adenocarcinoma, clearly not at the same level as HPV 18, is something for consideration. I don't know if you should put that in specifically, but certainly I think the IARC definitions of oncogenic types and what's included in this might be helpful.

DR. CALIENDO: Yes, Alan.

DR. WAXMAN: I think it's very important to specify that it's approved with the ThinPrep medium, not the SurePath medium.

And a very important caveat, not for the FDA but for those of us who will be in the business of educating providers, that lab-developed tests should not be used for these indications.

DR. CALIENDO: So let me just clarify, because I don't think we want to get into a discussion of LDTs. But when you talk about lab-developed tests, are you talking about off-label use of an FDA-cleared test with SurePath, or are you talking about laboratories actually having lab-developed HPV tests?

DR. WAXMAN: I'm talking about --

DR. CALIENDO: Because those are very different things.

DR. WAXMAN: Yeah, I know. I know. And I guess I'm talking about both of those -- in separate paragraphs, perhaps.

DR. CALIENDO: Okay. Yes?

DR. PORTIS: We talked before about education, and some of

that education is for the patient. And I don't know in what way this information will be disseminated, but we know that patients get lots of information now and sometimes don't understand what the changes are about.

And so I think patients have to be educated about what this does not screen for, and not just think about making sure the doctors are educated about how it's used or not used. But I think patients frequently have a misunderstanding. I mean, we see it with mammography, for instance, all the time. They come away thinking everything is fine when it's only a very specific thing that's fine or not fine.

DR. CALIENDO: Okay. So the CAP thing, let's go through this because I want to make sure we want to put all this in here.

So the first thing is about quality control. Being that this test is supposed to be performed in a CLIA-certified laboratory, do we feel we need to put any additional information in the package insert about that, or anything above and beyond what the FDA would typically do? You know, when I read that, to me, this was like, this is the way you do testing in a clinical lab. So I'm not sure -- go ahead.

DR. BURK: Robbie Burk.

So the World Health Organization does have proficiency testing, a panel that they use, and I don't know how that integrates or how that affects this or what the actual --

DR. CALIENDO: So labs are required to do proficiency testing -- I'm sorry, Angie Caliendo -- on every test that they do. This would be no different.

Go ahead, Beth.

DR. UNGER: Yes, this is Beth Unger.

And the WHO proficiency test is not for clinical applications. It's designed for epidemiologic monitoring for high analytic sensitivity, and it really would not be appropriate for this use in proficiency testing, and so I wouldn't recommend that. But proficiency testing of some kind will have to be available.

DR. CALIENDO: And my comment is, it already is because labs are already doing this test for a different indication. But the proficiency of the testing material is already available through the College of American Pathology.

Okay, so the next thing they talked about was HPV-negative cancer. And so is that something we want the FDA to put in the package insert, that not all cervical cancer will test positive for HPV?

(No audible response.)

DR. CALIENDO: Testing methodology. This one, I think, is another one of those where it's more of a concern of off-label use as opposed to the FDA stating this is the way the test should be used, this is the specimen type that should be used, this is approved for ThinPrep, and defining it rather

than -- I don't think you would say you can't use it in any other way, correct? You would just state how it should be used, but it's the same principle?

DR. SIMON: Yes, we state how it was used.

DR. NOLLER: I do think that some statement needs to be made, if it can be, about the lab-developed tests, because I was constantly amazed by patients who would come in from little hospitals -- I'm surprised they could do it, hematocrit and their pathway -- have developed their own HPV test and it was so good, they never made a mistake. There are so many of them out there, labs doing something, and I think some statement is very important.

DR. CALIENDO: Okay. Someone else over here?

DR. BIRDSONG: We're going to methodology again. Just to clarify. I think you're saying you would do it anyway, but you really need to -- I don 't know if you could -- I don't know if it's appropriate to modify other FDA approvals, but specify that primary cervical cancer screening -- you know, you have the data for this specific test or you don't have it; the others may work, but you don't have the data to support that.

And I think there is a significant likelihood of clinicians saying let's do the HPV test for cervical cancer screening without knowing which particular test is being done, and that could conceivably cause problems because you only have data for this one. And I think the wording or guidance should be issued from FDA to indicate that for right now, the only test that

you have that's been approved for primary screening is this one, and others will probably come along and you can add those to it.

DR. CALIENDO: Beth, go ahead.

DR. UNGER: This is Beth Unger.

I think, in this particular indication, when we're kind of shifting to HPV as the primary screen, the quality of the sample is absolutely imperative. There's going to be no other way to monitor it. And that's why I was saying that I think we really need to emphasize the collection media and the collection devices. And that's even apart from what's in the directions. So I think that's why it needs a separate reemphasis, that the indication was based on this kind of sample collection and you can't just assume that any kind of sample is going to work.

DR. CALIENDO: Great.

Okay, the last point made in this statement here is about having a triage algorithm and follow-up algorithm. And so I think we've made that point, that this isn't a standalone test; this has to be incorporated. There has to be some plan to follow the patient based on the result.

Anything else? Because I'm going to read these through so that they're in the record officially. But before I do that, does anyone want to add any addition?

(No response.)

DR. CALIENDO: Okay. So what I have is that colposcopy is not

indicated if HPV types other than 16 or 18 are detected; other high-risk types other than 16 and 18, they should go to the triage algorithm.

We have to clearly specify the appropriate collection devices, the collection media, specimen stability, that sort of thing.

A comment that this test is not appropriate for women who have undergone a hysterectomy.

It would be helpful to include the high-risk types that are in the WHO definition.

Reiterate that this is approved only for ThinPrep collection devices; that would tie back into the specific media.

I don't know honestly if a statement about LDTs can be made. Sally, I'll leave that to you whether something like that would be put into the package insert. I would say that has to go into educational material.

So there needs to be educational material both for physicians on follow-up and algorithms for follow-up; also, how the tests should be used and should not be used. And then, as pointed out by Natalie, patient education, what this test does and what this test does not do for the patient.

And then, finally, a comment that not all cervical cancer will test HPV positive.

Anything else?

(No response.)

DR. CALIENDO: Sally, do you have any questions?

DR. HOJVAT: No, that's been very helpful. Thank you.

DR. CALIENDO: Okay. So Dr. D'Agostino is still on the phone, and sorry, I forgot to ask you for your comments earlier. So please go ahead and add your comments.

DR. D'AGOSTINO: I didn't want to interrupt. I just want to make a couple of comments that -- statistics, so that's somewhere in the transcript. If you will indulge me for a few minutes.

I think that, number one, the data is very substantial. I think the data that the Panel is looking at, the advisory committee is looking at, and the presentations are, in fact, very substantial and very well laid out in terms of good sensitivity, the specificity. Even the safety issue, which is not as strong as the efficacy, but it's there. And I think we should be very comfortable with stating that.

I'm not concerned so much, but I think we should recognize an emphasis on CIN2 and CIN3 and so forth. And this is my lack of knowledge in the field, but in terms of the statistics, a lot hinged on that sort of sequence and that constellation and that when you vote, that's there and we're realizing it.

And number three, I think that there is a nice screening structure that's given where it talks about the HPV screening interval and the sequence of the testing that goes out, that I don't know that the age is substantiated in terms of hard science; but it's there and it's down to 25.

Let's see, clinicians on the committee made a much better argument than I can, that there is data there and recognizing that it's a moving target. But down to 25 seems to have some good justification; two-year interval, I think we have good justification.

I do think, "Now, what's the future; how do we know it's all there?" Well, like any screening, I've been involved with prostate cancer and so forth; we keep changing our mind and keep coming up with new data in terms of saying it's device screening interval, it's device screening test, and so forth. But that's those cost-type analyses, those effectiveness analyses, and it can be done after one puts this out as the primary method.

The other thing that sort of bothers me, but the other thing that I think we need to get off, we had a number of speakers talking about the co-testing as opposed to the sequential, and then also about the current guidelines being used. This is moving away from that, and I think again, I'd like to hear a statement. You've made a statement already, but I'd like to make a statement that we're very cognizant of that and understand the potential implications of that, but we think the data is substantial and the sequence that is being suggested does make sense.

And with those comments, I'll shut up.

Thank you very much.

DR. CALIENDO: Thank you.

Sally, is there anything else that we can clarify for you or

provide you with more information?

DR. HOJVAT: Not at this time.

DR. CALIENDO: So at this time the Panel will hear summations, comments, or clarifications from the FDA.

Do you have any comments to make?

DR. SIMON: Well, I do hope it's appropriate.

At this point, I do thank you all for being here. We're very happy to have this level of expertise at the table. The one comment I do want to make is that when we read the ballot questions, we would like you to take them quite literally in that for every question that ends with "is it safe for the proposed indications for use," "is it effective for the proposed indications for use," and the reason we ask you to take it very literally is because we have to per our regulations.

DR. CALIENDO: Does the Sponsor have any clarifying statements? It's not -- you couldn't present anything new at this point, but any comments you want to make.

MR. MAJEWSKI: Just very briefly. Thank you very much.

DR. CALIENDO: Okay.

MR. MAJEWSKI: So we just first want to thank the Panel members and the FDA for giving us the opportunity here today to present our case, and for a very thoughtful and well-balanced discussion of highly complex data, which brought our proposed indication.

We also want to thank the public speakers for their contributions today and for demonstrating their passion and concerns about how to best screen for cervical cancer.

So I would not want to forget the 47,000 women who actually enrolled in ATHENA and basically took the risk of being selected, 1 in 35, for colposcopy when they had a double negative test result, just to further the case of cervical cancer screening. So we really thank these women, as well.

So I think there are two subjects that I just very briefly want to touch upon. One is the safety concern. And I think Dr. Garcia, this morning, had on one of his slides -- do no harm, so I can tell you that we take it very serious. This is one of the reasons why we invested in a study with 47,000 patients to be able to show the safety of our test.

And while we heard that safety may not be as convincing as you would like to see, I just want to briefly repeat and reiterate that what you've seen today is that the cumulative incidence ratio in the population 25 and above for cervical cancer, for CIN3 and above, was .34. So that is compared to co-testing, which means that all the women in the same population, 25 and above, get the most rigorous screening that we know today, which is co-testing, where the cumulative incidence rate was basically .34. So from that perspective -- it is from my perspective -- only a small difference that we actually see in terms of the safety of the two algorithms.

So the second subject I would like to touch upon is just the

education part, because it came up a number of times, that every new indication will require education. And I can tell you that at Roche we are committed to support that with the professional societies and with the organizations. We want to basically drive the case in the marketplace. So to help to further the subject of education of the doctors, but also of the patients about the options that they have available.

With that, I just briefly would like to thank you again for your attention and for the great discussion and for considering our application for inclusion of HPV primary screening.

Thank you so much.

DR. CALIENDO: Thank you.

So before we go on to the vote, I would like to turn to our three representatives that will not be voting and give you a chance to comment, make any final comments that you would like to do.

So Glen.

MR. FREIBERG: Glen Freiberg.

Thank you, but I have nothing to add that I haven't already mentioned.

DR. CALIENDO: Cherie?

DR. SCOTT: Thank you, as well, and I have nothing else to add.

DR. PORTIS: Thank you. And I've made my points before. Thanks.

DR. CALIENDO: And I want to thank all three of you for taking time to come. Your contributions were extremely helpful, and we just appreciate your engagement throughout the day.

Okay, so we're going to need -- we're going to go on to the formal vote. They're going to need a few minutes to set that up, so we can talk amongst ourselves. Not about the Panel, of course. And as soon as they're ready, we'll reconvene and vote.

(Off the record.)

(On the record.)

DR. BURK: Thirty years of research in HPV funded by the American people, supported by the National Institutes of Health and other organizations has really culminated in our science, getting to the point of today. We were able to really evaluate a carefully designed study that was done in cooperation with the FDA.

As I can see, the FDA has re-analyzed the data, has controlled for certain variables or other factors in the study that we might not even have thought about. The data is presented. I think everybody in the Panel appreciates how far the science has come and that, from what I've heard, our decisions should be based on this body of knowledge that's been accumulated and from the data that was presented.

DR. CALIENDO: So I would just like to explain to the Panel that we're going to vote. We'll vote on all three of the questions, one right after

another: yes, no, or abstain. And Sara will explain to us how you're going to do that.

After that, I'm going to go around and ask each of you, for the record, to document how you voted. So just so you're not shocked after we vote, when I say Beth, tell me how you voted on the three questions -- if you vote no, the FDA would appreciate you giving the reason that you voted no. That will help them assimilate all this information.

DR. MASSAD: Can I ask a question?

DR. CALIENDO: Go ahead, Stewart.

DR. MASSAD: If we vote yes, can we still --

DR. CALIENDO: Absolutely. We in no way want to stifle anybody's opinions, thoughts, contributions.

I think the paper is for a backup in case of some sort of glitch, correct?

LCDR ANDERSON: Correct.

DR. CALIENDO: Okay, we got the double A team up here now.

Okay. So we are now ready to vote on the Panel's recommendation to the FDA for the cobas HPV Test. The Panel is expected to respond to three questions relating to safety, effectiveness, and benefit versus risk. LCDR Anderson will now read three definitions to assist in the voting process. She will also read a proposed indication for use statement for this device.

I want to make one other comment. I only vote if there's a tie, so just so you're not surprised, as we go around, that I am actually not voting.

LCDR ANDERSON: The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert Advisory Panel on designated medical device pre-market approval applications that are filed with the Agency. The PMA must stand on its own merits, and your recommendations must be supported by safety and effectiveness data in the application or by applicable publicly available information.

The definitions of safety, effectiveness, and valid scientific evidence are as follows:

Safety as defined in 21 C.F.R. 860.7(d)(1) - There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risk.

Effectiveness as defined in 21 C.F.R. 860.7(e)(1) - There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use,

when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Valid Scientific Evidence as defined in 21 C.F.R. 860.7(c)(2) - Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

The Sponsor has proposed the following additional indications of the cobas HPV Test. Currently approved indications will remain unaltered in the label if new indications are approved.

In women 25 years and older, the cobas HPV Test can be used as a first-line primary cervical screening test to detect high-risk HPV, including genotyping for 16 and 18. Women who test negative for high-risk HPV types by the cobas HPV Test should be followed up in accordance with the physician's assessment of screening and medical history, other risk factors, and professional guidelines. Women who test positive for HPV genotypes 16 and/or 18 by the cobas HPV Test should be referred to colposcopy. Women

who test high-risk HPV positive and 16/18 negative by the cobas HPV Test (12 other HR HPV positive) should be evaluated by cervical cytology to determine the need for referral to colposcopy.

Panel members, please use the buttons on your microphone to place your vote of yes, no, or abstain for the following three questions. Voting Question 1 reads as follows, okay?

Voting Question 1: Is there a reasonable assurance that the cobas HPV Test is safe for use in patients who meet the criteria specified in the proposed indications?

Please vote now: yes, no, or abstain.

(Panel vote.)

LCDR ANDERSON: Voting Question 2: Is there a reasonable assurance that the cobas HPV Test is effective for use in patients who meet the criteria specified in the proposed indications?

Please vote now: yes, no, or abstain.

(Panel vote.)

LCDR ANDERSON: Voting Question 3: Do the benefits of the cobas HPV Test for the use in patients outweigh the risks for the use in patients who meet the criteria specified in the proposed indications?

Please vote now: yes, no, or abstain.

(Panel vote.)

LCDR ANDERSON: Please give us a moment as we tally and

verify the official votes. Thank you.

(Tally of votes.)

LCDR ANDERSON: The votes have been captured, and I will now read the votes into the record.

On Question 1, the Panel voted yes that the data shows that there is reasonable assurance that the cobas HPV Test is safe for use in patients who meet the criteria specified in the proposed indications.

Total yes, 13. Total no, 0. Total abstain, 0.

On Question 2, the Panel voted yes that there is reasonable assurance that the cobas HPV Test is effective for patients who meet the criteria specified in the proposed indications.

Total yes, 13. Total no, 0. Total abstain, 0.

On Question 3, the Panel voted yes that the benefits of the cobas HPV Test do outweigh the risks for use in patients who meet the criteria specified in the proposed indications.

Total yes, 13. Total no, 0. Total abstain, 0.

The three voting questions are now complete.

For the record, I will list the voting members and their votes.

Unger: Question 1, yes; Question 2, yes; Question 3, yes.

DR. UNGER: Am I supposed to say yes, I did vote? No?

DR. CALIENDO: She's saying it instead. Sorry.

LCDR ANDERSON: This is for the record. Thank you.

DR. CALIENDO: We'll have a minute for comment in a minute.

LCDR ANDERSON: Saraiya: Question 1, yes; Question 2, yes; Question 3, yes.

Massad: Question 1, yes; Question 2, yes; Question 3, yes.

DR. MASSAD: So I have reasonable assurance that this --

DR. CALIENDO: No, wait. You're going to comment in a second, sorry. I confused you all. She's going to go around, read the votes, and then I'll come back and everyone will get a chance to comment.

LCDR ANDERSON: Birdsong: Question 1, yes; Question 2, yes; Question 3, yes.

Waxman: Question 1, yes; Question 2, yes; Question 3, yes.

Cain: Question 1, yes; Question 2, yes; Question 3, yes.

Burk: Question 1, yes; Question 2, yes; Question 3, yes.

Rand: Question 1, yes; Question 2, yes; Question 3, yes.

Hanson: Question 1, yes; Question 2, yes; Question 3, yes.

Noller: Question 1, yes; Question 2, yes; Question 3, yes.

Hillard: Question 1, yes; Question 2, yes; Question 3, yes.

Harrell: Question 1, yes; Question 2, yes; Question 3, yes.

Blumenstein: Question 1, yes; Question 2, yes; Question 3, yes.

Thank you.

DR. CALIENDO: Okay, so we're going to go around, and everyone has an opportunity to comment. And we're going to start with Beth

and just go around to the group, so Beth.

DR. UNGER: I want to thank the FDA and the Sponsors for presenting the issues so clearly because it was very difficult, the data was very complex. But I think in the end, the issues were made clear.

Thank you.

DR. SARAIYA: I want to thank everybody and just comment that I hope everything will work out ideally, as indicated, and the guideline groups follow through and make sure that the over-screening stops and we have an organized screening system.

DR. MASSAD: Stewart Massad.

The balance of safety and effectiveness depends critically on the screening interval. This is a powerful test with a very strong negative predictive value, and the likelihood of disease will be substantially less than in the data presented today in women who are screened at too short an interval after an initial negative screen. I can only hope that the professional societies that develop guidelines will pay attention to that as they develop the recommendations that will guide clinicians going forward.

DR. BIRDSONG: George Birdsong.

I would like to thank the Sponsor and the FDA for assembling and presenting all the data in a reasonably clear fashion. I do feel like the data presented are sufficient for safety and effectiveness. I do have some concerns, possible concerns, regarding safety that don't rise to the level that

would change my vote.

In particular, the data that was presented regarding prevalent invasive cancer certainly trends in the right direction, but it's numerically not very robust, and I realize that that's not really possible because there's not a lot of cancer, but given the results of other studies with HPV and prevalent invasive cancer, I would like to have seen more robust data supporting the performance of the test.

And then as others have mentioned, the performance of the test is long term, I think, critically dependent on -- let me back up. I won't say critically dependent, but can be much better described in the context of an organized screening system. In the United States, we have an opportunistic screening system. So those are things that are not yet resolved, in my mind. However, they don't rise to the level of prompting me to not vote yes.

DR. WAXMAN: Alan Waxman.

It was a very nicely put together study, and I thought the data basically left us little choice but to vote the way we did. The clinicians of the United States, and probably the rest of the world, now have three options for screening women, three very different options that have very different, potentially different intervals, different triage trees.

I think that the challenge is now there for the professional societies -- and I know SGO and ASCCP are actively involved in this -- to put together data-driven, evidence-based algorithms, to the extent that there is

data, and then go forward with robust education for providers and for patients. I think that women are going to be well served by having more choices, but it's going to be very interesting to watch the next several years as this rolls out.

DR. CALIENDO: George, you want me to reverse flow?

DR. BIRDSONG: Temporarily.

DR. CALIENDO: All right.

DR. BIRDSONG: Just wanted to add another concern; not with the proposal itself, but preventing off-label use. That doesn't affect how I would vote, but there is a potential for untoward things to happen.

DR. CAIN: So I appreciate very much the information and the way it was presented. I think I'm struck by the tremendous responsibility of the societies now to come up with common guidelines and, beyond that, to track what happens with those guidelines: Rather than just doing guidelines, is this the time for registry? Is this the time to understand how vaccination will change these sorts of proposals? So I see the future as a wealth of responsibility that needs to be stepped up to.

DR. WAXMAN: Mona is going to have a job for decades to come.

(Laughter.)

DR. BURK: I think that my decisions are based on the data that was presented in the ATHENA study; was built on three decades of public

investment in the National Cancer Institute and other institutes and NIH. I thought the Sponsor and the FDA did an excellent job of analyzing the data, presenting, so we could understand it. Looking at other variables that are involved to correct for particular biases, I think the negative predictive value of HPV DNA testing has been one of the strongest components of its use to really help us prevent cervical cancer in women, not only in the United States, hopefully throughout the world. This is about secondary screening. We also have primary screening. I think our ultimate goal should be, really, the prevention and elimination of cervical cancer.

DR. RAND: Well, I'd like to echo the sentiments and thank the FDA and the Sponsor for an excellent and clear presentation, and very complex issues and data. And thank the Panel for their interesting insights and comments, and hope that this leads the Sponsor to take pity on us who run laboratories and perhaps lower your pricing.

(Laughter.)

DR. HANSON: As another laboratorian, I echo that sentiment. I'll just reiterate what's already been said, that the presentations today were exceptionally clear, and I really appreciate how the data was presented to be able to make an informed decision. The professional societies have a lot of work ahead of them, as was mentioned previously. But the other thing I think we really need to see in the future, going forward, is cost-effective analyses as well, to really understand, from a laboratory perspective, not only what

patients' preferences are, longer-term outcomes, but also resource utilization and how that can be optimized.

DR. NOLLER: Thank you for the invitation to be here. I have nothing to add that hasn't been said, probably several times. Thank you.

DR. HILLARD: I would just echo the thanks as well as echoing the caveats and concerns that have been expressed so far, and I think it will be interesting times in the near future.

DR. HARRELL: Lizzie Harrell, ditto.

DR. BLUMENSTEIN: Nothing to add. Nice data.

DR. CALIENDO: Okay.

Oh, go ahead. Sorry, Glen.

MR. FREIBERG: Glen Freiberg.

I've been to a lot of these meetings over the years, and I want to take an extra minute to commend both the FDA and the Sponsor on their preparation and their presentations. They were really terrific.

Second, I'd like to address the Panel, not the FDA part of the Panel but the rest of the Panel, because you've expressed concerns about LDTs. Those of you that are involved in your professional societies, there are things you can do. The first I'd recommend is to try to compel those labs using LDTs to publish their cutoffs, their statistics, their clinical data, and their analytical data. You can do that to make that change, and until that happens, there's no way for you to interpret the LDTs. So if you have concerns, there's

a path you can take.

Thank you.

DR. CALIENDO: Okay. I would like to thank the Panel, the FDA, the Sponsor for your contributions today. This has been a long day, but I think a very productive day. I thank the Panel for coming so prepared. I, too, found the presentation of the data to be remarkably clear and made our responsibilities much easier. So thank you for that.

Sally, I don't know if you have any final remarks.

DR. HOJVAT: Yes. To thank you for being a very good chairman.

DR. CALIENDO: Thank you.

DR. HOJVAT: Woman. Thank you very much, Angie.

DR. CALIENDO: Okay. So the March 12, 2004 [sic] meeting of the Microbiology Devices Panel is now adjourned.

Thank you.

(Whereupon, at 5:30 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

MICROBIOLOGY DEVICES PANEL

March 12, 2014

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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