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P R O C E E D I N G S

Opening Remarks

DR. WILSON: Good morning. I'm Dr. Mike Wilson, Chair of the FDA Microbiology Devices Panel. I would like to welcome everyone to the meeting today. As the first order of business, I would like to turn over the meeting to Ms. Freddie Poole, our Executive Secretary, who will give some opening remarks.

MS. POOLE: Good morning and welcome. We just have a short reminder that all cell phones and pagers should be turned off. I would like also to read the following announcement for conflict of interest.

The following announcement addresses conflict of interest issues associated with this meeting and is made a part of the record to preclude even the appearance of impropriety. To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by the committee participants.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interest. However, the agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interest of the government.

A waiver has been granted to Dr. Robert Burk for his financial interest in a firm at issue that could potentially be affected by that panel's deliberations. The waiver allows him to participate fully in today's discussion. Copies of this waiver may be obtained from the agency's Freedom of Information Office, Room 12A15 of the Parklawn Building.

The agency would also like to note for the record that Dr. Evan Myers, who is a guest today, has acknowledged an interest with a firm at issue. The interest is in the form of a grant. In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him- or herself from such involvement and the exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

DR. WILSON: Thank you.

At this point, I would like the panel members to introduce themselves to the members of the audience starting with Dr. Wendel, please.

DR. WENDEL: I'm George Wendel. I am an

obstetrician-gynecologist from the University of Texas Health Science Center in Dallas.

DR. MYERS: I am Evan Myers. I am an obstetrician-gynecologist and epidemiologist from Duke University Medical Center in Durham, North Carolina.

DR. BURK: Hi. I'm Dr. Robert Burk. I am Professor in Microbiology and Immunology, Pediatrics and Epidemiology and Social Medicine at the Albert Einstein College of Medicine.

MR. REYNOLDS: I'm Stanley Reynolds. I am with the Pennsylvania Department of Health, Bureau of Laboratories. I am the consumer representative.

DR. FELIX: I am Juan Felix. I am a pathologist and cytologist at the School of Medicine, University of Southern California.

DR. HAMMERSCHLAG: I'm Margaret Hammerschlag. I am Professor of Pediatrics and Medicine and Director of Pediatric Infectious Diseases at the State University of New York, Downstate Medical Center.

DR. WEINSTEIN: I'm Mel Weinstein. I am a Professor of Medicine and Pathology at Robert Wood Johnson Medical School in New Brunswick, New Jersey.

DR. TUAZON: I am Carmelita Tuazon. I am Professor of Medicine and an infectious disease specialist at the George Washington University Medical Center.

DR. BERRY: Donald Berry, Chairman of Biostatistics at the University of Texas M.D. Anderson Cancer Center.

DR. BROWN: I am Carol Brown. I am Assistant Professor of OB-GYN at Cornell Wilde Medical School and a gynecologic oncologist at Memorial Sloan-Kettering Cancer Center.

DR. DURACK: Good morning. I am David Durack. I am an infectious-diseases physician working with Becton Dickinson. I am the industry representative on the panel.

DR. KOUTSKY: I am Laura Koutsky, Professor of Epidemiology at the University of Washington.

DR. MIRHASHEMI: Ramin Mirhashemi, Assistant Professor, University of Miami, gynecologic oncologist.

DR. GUTMAN: I'm Steven Gutman. I am the Director of the Division of Clinical Laboratory Devices, FDA.

DR. WILSON: Thank you.

Issue

DR. WILSON: I would like to read the issue of the day to everyone. The issue today regards the appropriate types of information necessary to determine the effectiveness of in vitro diagnostic devices that detect human papilloma virus when these devices will be used in conjunction with Pap smear in women 30 years or older to increase the effectiveness of Pap smear screening for

cervical cancer. Additionally, the panel is discuss and make recommendations on issues concerning the uses of HPV devices without Pap smear to determine a women's risk of cervical cancer and the use of self-collection and alternative specimen sources.

There will, of course, be not voting today because this is an issues meeting only where the FDA is seeking guidance from the panel members.

I would like to begin the presentations now because we are going to be on a fairly tight schedule today. We will ask that all of the speakers, again, as Ms. Poole has said, please identify any financial interest that they may have in any of the products being discussed today as well as please remind all of the speakers to honor the time that is allotted to them to speak today.

I would also ask the panel members to please hold all questions until after the presentations. I would like to remind the audience that all the panel members can ask questions of the speakers.

Our opening statement will be given by Dr. Gutman who is the Director of the Division of Clinical Laboratory Devices.

Steve?

Opening Statement

DR. GUTMAN: Good morning. As you have just been

told, the panel meeting today is one of a subset of advisory panels designed to look at general issues rather than specific products. FDA is hoping to utilize the expertise and experience of those present to provide sponsors with general directions and scientific recommendations on claims for human papilloma virus testing but not to consider a specific product approval.

The good news is that no one is required to vote. The better news is that you have an opportunity to help both the agency and future sponsors of diagnostic products in this area develop clear paths for approvals which will benefit the public health.

There are few diagnostic procedures in modern laboratory medicine as important or valuable as tests for cervical cancer. The Pap smear stands as a landmark in preventive medicine and public health. Without doubt, human papilloma virus testing has already contributed to better patient management.

FDA is clearly interested in the test's future untapped potential. We look forward to hearing from the group assembled here today on the scientific issues involved, on appropriate future expansions and test use, and in datasets to support those changes.

As always, the agency is challenged by the important balance assigned to it of setting appropriate data

thresholds, insuring reasonable labeling while enabling new technology to reach the medical marketplace in a timely manner.

The FDA Modernization Act dictates we do this using good science but following the least burdensome pathways. I pass that challenge on to you.

DR. WILSON: Thank you.

We would like to begin now with the industry perspectives on the issues. Again, I would ask the panel members to hold their questions until after all three presentations. The first scheduled speaker is Mr. Mark Del Vecchio, the Director of Regulatory and Clinical Affairs for Digene Corporation.

Industry Perspectives in Issues

Digene Corporation

MR. DEL VECCHIO: Good morning. Thank you very much.

[Slide.]

I would like to start off by thanking Dr. Gutman and the rest of the DCLD for giving Digene the opportunity to participate in the discussion of this very important topic.

[Slide.]

For those who are not familiar with Digene, we are an emerging growth company located here in Gaithersburg,

Maryland that develops and manufactures molecular-based diagnostic tests for infectious diseases. All of our work is directed towards improving clinical outcomes and containing healthcare costs.

We have several FDA-approved HPV tests that utilize the Hybrid Capture technology. We have spent the early part of the last decade developing and optimizing this fundamental technology and, in the later portion of the 1990s, validating its use in many large-scale clinical trials worldwide.

[Slide.]

The information that we are going to present this morning will focus on the technical aspects of HPV testing and the scientific evidence that supports its use as a general population screening test specifically in conjunction with the Pap smear for women age 30 and older.

Although we recognize cost effectiveness as an important element in this discussion, we will not address detailed economic factors of HPV testing related to general population screening.

[Slide.]

The six major topics we will be discussing this morning include the role of HPV in the diagnosis of cervical disease and cancer, clinical data requirements and results, applicability of foreign data to the U.S. population,

limitations of the current screening program, the importance of HPV in women's health and a response to questions that will be posed to the panel later this afternoon by FDA.

[Slide.]

With that, I would like to turn the podium over to our first speaker, Dr. Attila Lorincz, Senior V.P. and Chief Scientific Officer at Digene.

DR. LORINCZ: Good morning, everyone. One of my goals in the next twenty minutes is to provide you with some basic information relating to the role of human papilloma virus in human carcinogenesis of the uterine cervix. In addition, I also wish to explain to you the rationale for considering HPV testing as beneficial to an efficient cervical-cancer prevention program.

Finally, I will share with you the results of several large screening studies that demonstrate quite clearly the utility of HPV testing by Hybrid Capture II for the detection of high-grade precursors of cervical cancer.

[Slide.]

First, let's review some of the known facts about HPV infection. Virtually all malignant neoplastic lesions of the cervix, regardless of severity, are caused by one of the thirty genital HPV types. In fact, persistent infection with high-risk HPV is a necessary precursor of cervical cancer.

HPV is found predominantly in cervical cancers and precursors. In one particular study of 932 cervical cancers included in a worldwide comprehensive evaluation, 99.7 percent were shown to be positive for carcinogenic HPV types. Importantly, there are 13 HPV types as contained in the Hybrid Capture Probe B cocktail which account for the vast majority of the cervical-cancer-causing HPV types.

[Slide.]

Host-virus interactions are quite complex, but the key concepts are summarized in the schematic. Basically, it says that successful viral infection leads to HPV establishment and maintenance which can proceed to basically two outcomes. The first, shown on the left, is productive, typically self-limiting infection which generates infectious viral particles and generally leads to resolution of infection or removal by the clinician, but no neoplasia.

The second pathway, shown to the right, is one of long-term viral persistence over many years. A sizeable percentage of these particular infections may become malignant over time.

[Slide.]

The same HPV types detectable in cervical cancers are actually found in precursor lesions and in a small proportion of presumptively normal women over 30. This situation, then, fulfills one of the requirements of a good

screening program; namely, it should be possible to detect precursor lesions and to eradicate them before they become malignant. Clearly, an accurate HPV test can do that job.

Intervention is typically most effective at the level of high-grade precursor lesions such as HSIL, variably called CIN 2-3, which are 95 percent plus positive for one or other of the carcinogenic HPV types.

[Slide.]

So let's look at the question of HPV testing another way. HPV is a necessary cause of cervical cancer. Simply put, what that means is that if someone does not have an HPV infection, they are not of significant risk for cervical cancer.

HPV is a good marker of women at risk for neoplasia, as I will demonstrate in the data I will show you. Best medical practice does require identification of the etiological agent. I would like to emphasize that the Pap smear is not a test for HPV. The Pap smear is a test for morphological changes that may or may not be associated with an HPV infection.

[Slide.]

Looking now on the relationship of age with HPV in cervical cancer, we see that most HPV infections are transient. Peak prevalence occurs in women over age 30 and the likelihood of detecting persistent HPV increases as age

increases, therefore increasing the likelihood of detecting underlying cervical disease.

A positive HPV test result becomes more meaningful with increasing age because persistent infection with high-risk HPV is the necessary situation for the development of the precursor high-grade lesions in the cancers and, over time, the HPV prevalence is more likely to be persistent in older women.

[Slide.]

If we look at the relationship of age to HPV prevalence and incidence of cervical cancer, we see a number of interesting points, some of which I have made before, which is that HPV prevalence is very high in younger women. It declines with age down to, perhaps, 5 to 10 percent in women over about age 30. Cervical cancer is quite uncommon in women under 30, but increases to about a maximal value in the group aged 40 or above and slightly increases thereafter.

So this suggests that HPV screening might have its greatest utility in women at the older age groups where the positive predictive value of the test is going to be optimal. We suggest that that age is 30 years or older.

[Slide.]

Many organizations have, in fact, in the past, recognized the potential utility of HPV. ACOG, in 1993,

recognized the potential utility of HPV testing in conjunction with cytology which should be evaluated prospectively.

However, at that time, there was generally also a fairly strong negative sentiment about the use of HPV testing. I do recall presenting to the FDA panel approximately ten years ago on ASCUS triage and, at that time, the majority of the medical community thought that it was a really bad idea.

Yet, here we are with HPV as a recognized mode of ASCUS triage which is well-accepted. Currently, in the U.S., approximately 20 percent of women are triaged with HPV and that number is growing quite quickly.

[Slide.]

So let's talk about the screening trials. Since the time of the ACOG statement, a large number of international screening trials have been conducted. U.S. trials, for the most part, have focused on ASCUS triage and on natural-history studies.

[Slide.]

Let's look at some of those ASCUS triage studies. I have culled out three here from a larger number because they are fairly representative of what we see. Some of them represent smaller numbers from earlier studies and the yet-to-be fully-published ALTS study has a much larger number of

cases of high-grade disease.

In all cases, what we see is that the sensitivity of the HPV test is higher than the sensitivity of the Pap smear. This last test here, the last study, the ALTS study, actually used liquid cytology whereas the previous two used either conventional--and, in the Kaiser study, they used either both liquid and conventional cytology with similar results.

Focussing in on the specificity, we see that in two of the studies, the specificity of HPV testing and the specificity of the Pap smear were fairly equivalent.

[Slide.]

Focussing in now on the meaning of an HPV-positive result in cytologically normal women at baseline, this is an interesting study that was published recently that looked at 22,000 middle-socioeconomic women who were normal at baseline. The idea was to follow them up for several years in order to determine, among other things, what is the risk of a women who is HPV-positive or HPV-negative at baseline developing subsequent significant disease.

[Slide.]

The results that were presented and published are that there is an elevated risk of future cervical neoplasia associated with HPV infection in cytologically normal women. In fact, two-thirds of women who developed HSIL were HPV-

positive at enrollment and diagnosis and there was a 13-fold increased risk of developing HSIL in women who tested positive for HPV at enrollment.

We feel that these data, among others, demonstrate that natural history of HPV infection in the United States and is consistent with findings in international studies.

[Slide.]

I would like to show you some of the screening trials that have been underway. This represents a fairly complete, but not totally complete, list representing over 100,000 women, most of whom are undergoing or have completed trials with the Hybrid Capture technology.

[Slide.]

The basis for the selection is shown as follows. We selected six studies based on criteria appropriate to establish safety and effectiveness. These studies represent the entire study set and were not picked to be favorable in any way to the proposition of HPV testing for screening programs.

The results are consistent across all studies and I would like to emphasize and underline that these are new data previously unavailable to any group assessing the utility of HPV testing for screening including the high-tech HTA assessment performed in the UK or to the CDC.

[Slide.]

The criteria in these studies were as follows. They had ethics-committee approval with informed consent. The use of the Hybrid Capture test in all cases. Cytology performance was, in most cases, optimized. There was expert review of cytology or there was a strategy designed to improve the quality of cytology prior to the study in at least four of the studies so they represent best-case scenarios.

Each of the studies are individually statistically meaningful with racial and geographic diversity and relevant population characteristics applicable to the U.S. population.

Finally, we recognize that publication bias is present in all published studies and so we took all of these studies, including those that have been previously published, and we reanalyzed them in a uniform, consistent manner in order to try to eliminate any publication bias that might be inherent in the datasets.

[Slide.]

These are the data that are observed from these particular studies. Firstly, I would like to say that, with the exception of the Asian study, all of the studies represent relative sensitivities and relative specificities. By that, I mean specifically in the Asian study, we have absolute sensitivities and specificities because every women

in the study underwent definitive colposcopy with multiple biopsies so the parameters here are absolute results whereas, in the other studies, there is some inherent verification bias in that the double negatives were not followed other than a small percentage who were sent to colposcopy, really, for control purposes.

However, we feel that relative sensitivities and relative specificities are still accurate, valid and important because they represent the difference in sensitivity and specificity between two specific tests that are being compared.

So if we look now at the studies more closely, we see that, in all cases, the sensitivity of the HPV test was quite a bit higher in some cases, substantially higher, than the Pap smear. For example, in the Western European I study, Pap had a sensitivity of 34 percent versus 91 percent for HPV.

If we look at the combination of the tests, HPV-positive, Pap-positive, we see that, in all cases, the sensitivities are higher than the sensitivities of either test alone which might, actually, be expected by combinations of tests.

Looking now at the specificities of these particular tests, we see that specificity of the Pap smear is, in most cases, somewhat higher than the specificity of

the HPV test with the exception of the Asian study where the specificity of the Pap was quite a bit lower than the specificity of the HPV test. This, incidently, was also the only study that used liquid cytology.

If we focus on the Pap-plus/HPV combination, we see that the specificities are minorly reduced in most cases from either the HPV test or the Pap alone suggesting that these are actually quite a good combination of potential test results.

[Slide.]

Focussing in, now, on the positive predictive values and negative predictive values for these studies, a number of features become evident. The positive predictive value of either Pap or HPV or HPV-plus-Pap for high-grade disease or cancer is pretty much equivalent being on the order of 12 to about 25 percent.

If we look at the negative predictive values, the negative predictive values for HPV are, in all cases, higher than the negative predictive values of the Pap alone. I would like to emphasize that negative predictive value is not a tremendously good measure in cases where the disease is fairly rare because it appears as if there are fairly small differences, for example 99.3 versus 99.9.

But I would like to emphasize to you that these small differences are, in fact, extremely important because

they represent quite a large number of cases of disease that may be missed simply by a small change such as 99.3 to 99.9.

Furthermore, if we look at the combined negative predictive value of the two tests, we see that, in four of the six studies, the negative predictive values are 100 percent including the study in Asia where we have absolute representation of the results.

One last point I would like to underscore from this slide is that the estimated high-grade disease prevalence in the United States is about 1 percent which is very similar to prevalence in four of these studies. So I submit to you that the data represented by these studies, especially the top four, are very similar to what one would expect with an HPV test being used in a screening program in combination with the Pap smear.

[Slide.]

I would like to make a number of general conclusions from these data, then. First, the sensitivity and negative predictive value of HPV is always greater in the Pap smear. Furthermore, when you combine the tests, the sensitivity improves as does the negative predictive value regardless of race, income level, healthcare system, et cetera.

The sensitivity of HPV, generally being on the order of 84 to 98 percent, whereas cytology has a very

highly variable sensitivity. Specificity of HPV is slightly lower or equivalent or, in one case, superior to the Pap smear. The positive predictive values are similar for both HPV and Pap.

[Slide.]

Focussing in on the negative predictive values, we see that, in four of the studies, the combined negative predictive values for Pap and HPV were 100 percent. We feel that this minimizes missed disease attributed to variability of cytology and makes for a better screening program.

[Slide.]

Why are these data applicable to a U.S. population? They represent geographically and racially diverse compilations of data from various socioeconomic groups and cultures.

[Slide.]

The Paps, in most cases, were read by expert U.S. pathologists--in three studies they were read. The relative improvement in the sensitivity of the HPV over Pap is applicable despite differences in disease prevalence. The positive and the negative predictive values for these studies are very similar despite variations in disease prevalence.

[Slide.]

We feel that these data are strong in multiple

ways. They encompass multiple independent studies, each of which can stand on its own, together representing over 32,000 women.

Most studies were designed to maximize the sensitivity of the Pap smear and, in all studies, the presence of HPV is a more sensitive indicator for identifying underlying disease than the Pap smear.

[Slide.]

I would like to finish my talk with a number of statements that were made by joint experts at the EUROGIN meeting in Paris in April, 2000. The conclusions were among the following. HPV testing is objective and highly reproducible. It has a very high negative predictive value approaching 100 percent. It is highly sensitive, being on the order of 95 to 100 percent. Testing for HPV is a more effective primary screen for women over 30 than cytology.

Thank you for your attention.

With that, I would like to hand you over to Dr. Thomas Cox.

DR. COX: Good morning.

[Slide.]

First, my confessional. Unfortunately, I do not have any stock in Digene. I have received HPV testing support for various studies in the early 1990s for some of the clinical utility studies I did on HPV testing and ASCUS

patent management and, over the last few years, have occasionally served on the Scientific Advisory Board for Digene or on their Speakers Bureau.

Many of you know that, for the last twelve or so years, I have been very involved in trying to understand how to better improve our cervical cytology screening program. Many have asked me over this period of time why I feel that there needs to be a change when the incidence and mortality of cervical cancer has reduced so significantly, in the range of 70 to 75 percent.

I think that what I would like to present to you here are my thoughts on the cytology screening program, where I see that there are problems and where I think that HPV testing can help clarify those issues.

[Slide.]

Basically, most of the problems that I see the revolve around cervical cytology is that it is not an objective measure. It is a very, very subjective test. There are certain elements to that subjectivity that we can see in various studies. One in interobserver variability where more than one pathologist reading the same slide may come up with a different reading.

Obviously, that will lead to misclassification meaning that some Paps are read as normal when they may be abnormal or some are read as abnormal when they are not. Of

course, ASCUS as our equivocal group, is our most difficult area and the biggest thorn in our side.

I would like to comment on each of these in a minute.

Then we have a false-negative rate that has been documented in multiple large metaanalyses in the last few years as being much higher than we had originally presumed. When you add that in with the problems of patient compliance and a lot of people not being screened, it has resulted in us trying to have Pap-smear-screening intervals that I believe are much more frequent than are beneficial to either women or society; that is, annual Paps.

[Slide.]

So I would like to discuss each of these in order. I think the best interobserver variability study was done by Mark Sherman and Mark Shipman, and others, in which they took 200 atypical Paps and sent them to five very expert cytopathologists who read these Paps blinded to each other.

You can see on here that probably the most striking finding was that not a single ASCUS pap was agreed upon by all five as being ASCUS. This is a very equivocal category and it is very difficult for individuals to agree on it.

Secondly, and I think the most important, is that, for the first time, clinical utility of HPV testing was

shown in that all Paps were agreed upon by all five as LSIL or HPV-positive; that is, if we superimpose a more objective test on a subjective test, it can help clarify what is really going on.

If you look at this, you can see in what is called the cytologic certainty scale that the more pathologists in agreement, here, the more likely it was to be HPV-positive, this being an HPV-positive percentage here.

Those epithelial changes that were not related to precancerous changes or to HPV that might lead to a precancerous or cancerous change, those epithelial effects that are due to life and whatever were the ones that were very hard for the pathologist to agree on and they were more likely to be HPV-negative.

So it would appear that HPV testing in this setting could sort these issues out.

[Slide.]

Now, as we have already said, if a pathologist's LSIL is within normal limits, or another is ASCUS, we are going to have misclassification of LSIL, or ASCUS or any of the other Pap categories. In this large screening study from Kaiser in the mid-1990s, with Hybrid Capture II, you can see that, under the age of 30, 93 percent of the women tested positive for either low or high-risk HPV types.

This means that LSIL is a very effective marker

cytologically for HPV disease in young women. However, as women get older, you can see that the HPV positivity level drops and that this, I do not believe, is due to the fact, as some people have said, that HPV is detected less well in older women.

I believe it is due to misclassification of epithelial effects that are due to aging and to loss of estrogen and that can be very confusing, and the cytopathologist, then, may overread these Pap smears as HPV-related when they are not.

This creates great anxiety and undue costs in terms of follow up.

[Slide.]

If we look at the study out of Britain by Giles in single mildly dyschoreatic smears and look at women under the age of 35, in the green are the women that were not found to have disease at colposcopy. You can see that, typically, for young women we can't find disease with the LSIL referral about 30 percent of the time.

But in women who were over the age of 35, in this study, they could not find disease 65 percent of the time. I believe most of this noncorrelation is due to misclassification of these cytologic abnormalities as LSIL when they really are not HPV-related.

So, as David Leusely, President of the British

Colposcopy Society said in 1998, "There is an increasing concern that the disease that we are trying to prevent may not be well served by the current screening program because of poor specificity of the screening process."

We always talked about how specific the Pap is but I believe that, because our threshold has been set continuously lower and lower in terms of calling an abnormality, that specificity has really eroded.

[Slide.]

If we look at our program of ASCUS, we can see that, because cytology is subjective and that there are cellular changes that we can neither classify as definitely normal or as definitely abnormal, there are a large number of abnormal Paps that are really equivocal and actually outnumber, by a great deal, all of the other abnormal Paps in our system.

This has also driven excessive costs over the last few years and it is my strong belief that the ALTS data and other studies support the use of HPV testing in sorting this problem out. We are really finding who is at risk for having high-grade disease and who was likely to be normal.

[Slide.]

But these problems have prompted Laura Koutsky, who is on our panel here, and Nancy Kiviat to state, in the Journal of the National Cancer Institute in 1996 that,

"Although our current approach to cervical cancer control has been successful in lowering mortality rates of cervical cancer, it is widely acknowledged to be inefficient and costly." It has reduced the rate of cancer but at a high cost.

[Slide.]

Now that we know that HPV causes cervical cancer and its precancerous state, the idea would be to remove from the screening system all who have abnormal Paps but do not have HPV as a cause to remove the subjectivity of the present screening system.

[Slide.]

In terms of false-negative rates, as you all know, the AHCPR came out with this test in 1999 looking at over 600 studies in the literature and made the statement that, "The conventional Pap test is less sensitive than it is generally believe to be," and that average sensitivity for cervical disease was 51 percent and specificity 98 percent.

I believe that, more than likely, for high-grade disease, we are probably looking at 70 to 75 percent sensitivity for the conventional Pap.

Fahey, et al., in 1995, did a metaanalysis which some have criticized but he found that the Pap had a mean sensitivity of 58 percent and a mean specificity of 69 percent in screening samples. A study by Nanda and Evan

Myers and others, some of the same Duke group, that came out in the Annals of Internal Medicine this summer made the statement that, in their study, the results were generally consistent with those of the Fahey study.

So now we have an increasing body of evidence putting the sensitivity of the Pap-smear level much lower than what we had originally thought.

[Slide.]

What is the effect of poor sensitivity of screening intervals? Obviously, if we feel uncomfortable about missing high levels of disease, we are going to want to screen more frequently. ACOG recognized, in 1995, that their three-year screening interval between visits may be too long due to limitations of the Pap smear.

A high number of false-negative results and failure of patients to return at regular intervals were their reasons for this.

[Slide.]

Kaiser Permanente has looked at this issue in their Guidelines of 1996 and printed this actual analysis in which they looked at the estimated cases of cervical cancer per year in the KPNCR, that is the Kaiser Permanente Northern California Region, with Pap intervals of 1, 2 and 3 years projected on the results of the IARC metaanalysis and several of its subunits that contributed to that analysis as

well as the Western Washington study which was separate.

You can see the number of cancers projected per year in the Kaiser Northern California Region on the basis of one, two and three-year screening intervals shows that there is anywhere from a three to four times increased rate of cervical cancer going from two to three years.

Indeed, that is in line with the AHCPR which estimated that annual screening would result in about 100 cases of cervical cancer per 100,000 women over a lifetime versus 500 cases over a lifetime for three-year screening intervals. That is almost a five times increased rate of cervical cancer.

That is not inconsequential no matter how we look at cost of live years saved.

[Slide.]

So, on the opposite end of the spectrum, we are being asked to increase our screening intervals to two- to three years by many organizations, as we can see here. But I think that several of them have put the statement at the bottom here that, high-risk women should be screened more frequently than low-risk women.

That puts a big burden on the clinician and I think is the reason why many clinicians, in fact most that I poll, don't seem to be adhering to longer screening intervals, because they can never tell who is really low

risk because they never know the other half of the equation, and that is the male side of the history.

[Slide.]

Not knowing, that, we don't really know who is low risk. We need some other marker to tell us who is low risk. I believe HPV testing does that. The reason that it does that is if it gives us a negative predictive value of nearly 100 percent and also can predict, over the next few years, that the person is not likely to get significant disease, then we have truly identified women as being low risk and can go to a longer screening interval.

The major obstacle to widening screening intervals is false-negative Paps. I think we can virtually eliminate that issue by combining it with HPV testing.

[Slide.]

This is an algorithm that I feel would work. Many ask, how would we possibly use these two together. I think if we tested for cytology and high-risk HPV and we had a normal Pap and a positive HPV test, these women are at increased risk of either having disease now or in the near future and, therefore, they should have an HPV and Pap test follow up in somewhere between six and twelve months.

Either the Pap abnormal or a positive HPV test continued at that time indicates increased risk and they should be evaluated by colposcopy. But, if they are HPV-

negative and normal, they have really likelihood of having disease or in the next three years and they should be reliably sent to the three-year follow up without concern about disease developing during that time frame that would be at risk for them.

If they are ASCUS HPV-positive, they should go to colposcopy. ASCUS HPV-negative, really, is essentially similar to benign cellular change and should be considered within normal limits and put back into an annual screen until they have a normal Pap at annual. Then they can go to further screening intervals.

LSIL-positive refer to colposcopy. LSIL-negative, low risk of disease. HPV and Pap follow up in six to twelve months. HSIL, whether HPV-positive or negative, should be sent to colposcopy. I think it is a relatively uncomplicated system and could be utilized by virtually any clinician in the United States.

[Slide.]

So what is a woman's viewpoint? Basically, women do not want to get or to die from cervical cancer. But they don't want to be abnormal either. They want to feel normal and I believe that, on an annual screening basis, we have many chances, over a woman's lifetime, of getting an abnormal Pap that makes them not feel normal.

[Slide.]

On the other hand, I would also admit that neither a positive Pap test nor a positive HPV test is normal. However, reducing the number of screens in a woman's life decreases the overall risk of having a positive test even when you are double screening.

[Slide.]

So, overall, I believe that HPV testing may decrease anxiety associated with cervical screening for several reasons. One, women can feel more reassured that they are not likely to get cervical cancer because of a negative predictive value of nearly 100 percent. Secondly, the decreased risk of having a false-positive test during one's lifetime relative to annual screening should reduce overall anxiety.

And I believe that this is a better screening program. So, during the course of today, I would be very happy to answer questions that you all may have regarding this. Now it is Mark's turn.

MR. DEL VECCHIO: Thank you, Dr. Cox. I will make this as quick as possible.

[Slide.]

Based on the strength of the data and information just presented, I would like to just briefly, like I said, highlight Digene's intended regulatory course in seeking approval for expanding the intended use of this test.

[Slide.]

Broadly defined, the Digene HPV test is used for qualitative detection of HPV DNA in cervical specimens. Two of the main intended uses, as Dr. Lorincz has indicated, ASCUS screening for colposcopy referral and management of women with high- and low-grade disease.

[Slide.]

The broadened intended use that we have proposed to the agency is as follows: as an initial general-population screen for women age 30 and above in conjunction with the Pap smear to determine the likelihood of high-grade cervical disease and the need for appropriate follow up at the discretion of the physician.

I would like to reiterate that we are not suggesting that, based on the data presented this morning, that the HPV test will be a replacement for Pap.

[Slide.]

In order to adequately support the expanded intended use, we have performed a prospective analysis of the existing data in the six studies described by Dr. Lorincz to determine performance of HPV and Pap combined. We intend to demonstrate that the studies chosen are sufficiently applicable to U.S. populations.

Accordingly, we will submit the scientific evidence as the PMA supplement to demonstrate safety and

effectiveness for the proposed intended use. And I wanted to emphasize that, based on the supporting scientific evidence, that the test offers significant advantages when used with existing approved alternatives.

Accordingly, we feel FDA should place high importance on such a submission due to the public-health implications of not doing so.

[Slide.]

I wanted to take this opportunity to address the specific questions that DCLD will pose to the panel later on today. Criteria that we believe should be developed to support an HPV screening claim for women 30 and over include large-scale prospective clinical trials that designate women at increased risk of developing cervical disease by identifying underlying cervical disease, that the test performance shows an increase in sensitivity over Pap-alone with only a minor decrease in specificity.

We believe these should result in a diagnostic algorithm that does not introduce additional patient management risk into the screening program. In fact, this is an appropriate approach, we feel, since, rather than removing the current safety net, if you will, it is strengthened by adding an effective complementary test.

We feel that the six studies that we are considering and the proposed algorithm do, in fact, meet

these criteria.

[Slide.]

Looking ahead with respect to HPV screening without Pap, the data clearly indicate that sensitivity and negative predictive value of HPV alone is higher in all cases than Pap alone with no change in positive predictive value and only a minor decrease in specificity.

However, Digene's position remains to seek an adjunctive general-population screen for our HPV test at this time.

[Slide.]

As evidenced from the algorithm discussed earlier by Dr. Cox, the primary goal of properly interpreting HPV test results used in the screening modality is the identification of women at increased risk for underlying high-grade cervical disease and to identify women at little or no risk in order to safely lengthen the screening interval within current recognized guidelines, as suggested by Dr. Cox.

This allows a concentration of resources toward women at risk for disease and, again, represents a better screening algorithm to detect more disease at the outset.

[Slide.]

One brief statement regarding the use of alternate specimen types for HPV testing. I want to emphasize that

our current test utilizes physician-collected cervical specimens and that, although data is available for self-collected vaginal specimens, we do not feel that there is adequate data at this time to introduce this specimen-type for HPV testing in the U.S.

[Slide.]

Regarding the types of clinical data appropriate to support the use of HPV for screening women 30 and older, FDA, as Dr. Gutman indicated, should consider the least-burdensome approach to demonstrate the role HPV plays in improving the ability to detect underlying high-grade disease when used with Pap in this modality by the use, of course, of well-controlled prospective studies meeting the criteria that was discussed earlier.

Whether these tests were performed in the United States or internationally, they should demonstrate performance of HPV plus Pap versus cytology alone and represent relative population characteristics that are applicable to a U.S. population.

[Slide.]

The resulting labeling that comes out of these studies should clearly communicate performance data and population characteristics of the medical community. When international studies are used, the relative improvement in the ability of HPV and Pap together in identifying disease

compared to Pap alone is clearly applicable to the United States, we feel.

[Slide.]

It is important to note that studies should be designed considering that neither HPV nor Pap diagnose disease. Rather, together, they improve identification of current underlying disease and identify women at increased risk of developing disease to better direct colposcopy and biopsy. It is based on these procedures that definitive diagnosis made.

With that, I would like to thank everyone for their attention. We strongly believe that this information is very important for women's health both now and in the future.

Thank you very much.

DR. WILSON: Thank you.

Before we move to a brief question session, I would like to have Dr. Koutsky and Dr. Myers state for the record that they did not collaborate with Digene for the presentation and that the publications that were mentioned during the presentation are part of the public record.

DR. KOUTSKY: I have not collaborated with Digene. I am on the NCI-sponsored ALTS trial which uses Digene products. I also use the laboratory that does the testing, uses Digene products as well.

DR. MYERS: The publications that were cited were funded by the former Agency for Healthcare Policy and Research, now the Agency for Healthcare Research and Quality, the agency formerly known as the HCPR. I have received an unrestricted grant from Digene to evaluate cost-effectiveness issues of ASCUS triage but those results have not been published nor cited here.

DR. WILSON: Thank you.

In an attempt to keep us as close to the schedule as we can today, I would like to have a brief question session now from members of the panel for Digene. But we are going to have to limit this to just a very few minutes. Who would like to begin? Dr. Durack?

DR. DURACK: I have a question for Dr. Lorincz. You made it clear that you are not proposing the HPV as a stand-alone test at the moment but, hypothetically, if it were used as a stand-alone test for screening, what interval would you argue for, what frequency?

DR. LORINCZ: I hesitate to comment on that particular point because we haven't really taken that under significant consideration at this point in time. But I would just make a side comment that might be relevant which is that, if you look at the two tests, the majority of the sensitivity, by far, comes from the HPV test. If you combine the Pap, the improvement is fairly small.

So if one were to hypothetically eliminate the Pap smear, which we are not proposing, I would not significantly alter the intervals that we are suggesting here. There may be a proposal to perform Pap smears only on HPV-positive women as a more accurate form of follow up. That might be one possible strategy.

So we wouldn't conceive of eliminating the Pap smear completely in any event at this point in time.

DR. WILSON: Dr. Berry?

DR. BERRY: Just to follow up on that, you have given sensitivity of HPV alone and Pap alone and the combination, but you have not given sensitivity for any sequencing, for example the one you just gave, or also for the Cox algorithm, the sensitivity and specificity of that, which is a sequential--

DR. LORINCZ: The sensitivities and specificities are basically cross-sectional at this point in time. They do not attempt to add up the idea of disease that is present in an HPV-positive group that is cytological normal that is followed up more frequently than an HPV-negative group.

So I don't want to speculate on what that might be. I would suggest that the relative sensitivities of the HPV test, because it catches women who are at risk of future disease much more effectively than Pap would actually be accentuated.

But, to do that, I think requires some very sophisticated modeling which we have not attempted to do at this time.

DR. BERRY: Just one follow up. It is not clear to me that we, as a matter of public health, should be simply adding tests. We ought to be looking strategically at what is the appropriate configuration of the tests which might be dropping tests or using them in sequence.

DR. WILSON: Dr. Felix?

DR. FELIX: I want a clarification on the data that you presented regarding the studies, the Western European, Latin American and Asian studies. The sensitivity is for high-grade disease; is that correct?

DR. LORINCZ: The sensitivity is for CIN 2,3 or cancer in all cases; that's correct.

DR. FELIX: Is that also true for the specificity of the HPV test?

DR. LORINCZ: That's correct; yes.

DR. FELIX: Is that also true for the specificity of the Pap?

DR. LORINCZ: Yes; they were all used according to the same criteria. In other words, low-grade disease that was present was counted in the normal category. So if it were positive for Pap or HPV, as a final diagnosis, it would have been counted against the specificity.

DR. FELIX: So I am correct in assuming it is for high-grade disease only.

DR. LORINCZ: That's correct; yes.

DR. WILSON: Dr. Brown?

DR. BROWN: I have a question for Dr. Lorincz also about the data that you presented. You selected--Digene selected six studies out of a potential fourteen that you had listed. I noted that you did not include the study that you have listed that was done in the United States to look at this test as screening.

I was wondering why you did not include the data from the United States study and if there are going to be other studies that have been done in the United States in a similar fashion.

DR. LORINCZ: The reason we did not include the study done in the United States was that it was a very small study. It was actually done in Baltimore. There were very few cases of high-grade disease, the endpoint that we were interested in, so we chose to skip it. But it is actually available. It has been submitted for publication and it did show an extremely high sensitivity for the HPV test and a very sensitivity for the Pap smear on the order of, or exceeding, the differences that we have shown in the other studies.

DR. WILSON: Dr. Burk?

DR. BURK: I have a few questions. One, since we know that HPV persistence is a critical risk factor, can you comment on the potential role for detecting the persistence and for the role of specific types in HPV screening. I will do my questions one at a time.

DR. COX: Obviously, when we are talking about follow up of Pap-negative but HPV-positive women we are really looking at a system in which we want to evaluate persistence of virus and we know, as all of the studies have shown, that persistence of the virus is the main marker for development of hybrid disease. It is the necessary marker for it.

The present panel, as it is done, does not do type-specific testing so, from a persistence standpoint, that is a disadvantage. Attila might answer whether there are any plans in the future to do any type-specific testing out of this panel but, certainly, when we are looking at trying to prove whether detection of virus is a type-specific nature, having a type-specific test would be helpful.

DR. LORINCZ: The main criterion driving the lack of a differentiation between types and combining them into a panel is cost-effectiveness. It is simpler to merely do a positive versus negative test. The technology is available to differentiate and, at some point in time, to be decided

if there is a recognized utility for type stratification that is recognized to be cost-effective as well as clinically effective, then I believe at that time, it will be appropriate to consider specific typing.

DR. COX: Otherwise, I guess we would just be looking at positive-positive as a risk factor and we would have to act upon it on that basis rather than worrying about types, and acknowledging that some people will be getting different types and we will not know that.

DR. BURK: My next question, Dr. Cox, in your presentation, you talked about the negative predictive value. Also, Dr. Kusak, in his health-assessment report, lists out of one of the potential roles in HPV screening. Dr. Lorincz, how come you have not included the use of negative predictive value of an HPV screening test to increase the interval of screening in your, I guess, suggested uses of an HPV screening test?

DR. COX: I actually thought Atilla did, but may he didn't mention--I think he left the role of me taking about the screening intervals.

DR. LORINCZ: I did present negative predictive value actually a number of times and did emphasize that the negative predictive value of an HPV test is so high that it could potentially lead to an increased screening interval.

I guess the only point missing from that would be

the combined negative predictive value of the cross-sectional data plus the future risk of cervical disease. If you look at the group that is HPV-negative over a period of time, that is going to adjust the negative predictive-value estimates from a point prevalence to a longitudinal situation. But we haven't done that modeling.

But we are recommending that Pap-negative, HPV-negative, women go to a lengthened screening interval of three years because we feel that that is very safe. So, in that sense, the combined negative predictive value and Pap and HPV is the most important factor that we are using to suggest that lengthening.

DR. BURK: One last question. Dr. Cox and Dr. Lorincz, in your analysis, you group high-grade disease. From my understanding, HSIL and LSIL were really developed as a screening test in cytology and that diagnosis is really based on criteria CIN 1, CIN 2, CIN 3. Many of us in the field have kind of been grouping CIN 2 and CIN 3 together.

Could you comment on that, on the rationale of group CIN 2 and CIN 3 and calling it HSIL as a diagnostic category versus its intended category?

DR. COX: I think this is one of the things that Bethesda 3 in May of this year is going to really tackle. I do believe that putting together CIN 2 and CIN 3 in a diagnostic, as you say, cytologic category which is not

diagnostic, but grouping them together when often the cytologic changes, CIN 2, really behave, I believe, more like CIN 1 than they do like a true cancer precursor, CIN 3.

It would be my preference to see the CIN scale parted on the right-hand side, or left-hand side, whichever of the scenarios, so that you group CIN 2 and 3 like the Europeans do and CIN 3 on the other side. I think that reflects more the risk factors that are relative to what we will find at the time of colposcopy.

But those are issues, I believe, that Bethesda 3 is going to look at and that the ASCCP and others are banding together to do a consensus conference on the NIH campus in early September on management issues. I believe that is another issue we are tackling as well.

DR. LORINCZ: I just want to interject very briefly. Apart from the theory of improved categorization with respect to putting CIN 2,3 in CIN 1 or CIN 3, from the very practical perspective, I would like to emphasize that we were following in our analyses what is the currently accepted standard in the United States today for categorizing CIN 2, 3.

If we split those out, which we have in some of the studies, we found that the positivity rate of HPV for CIN 3 is at least as high, if not higher, than for CIN 2 and so, therefore, if one perceives that the CIN 3 is the more

important disease, restricting it to that endpoint would, in now way, jeopardize the quality of the HPV result that will be generated.

DR. COX: We found that in the ALTS trial, that the detection by HPV testing for CIN 3 in almost all instances seemed to be 2 or 3 percent higher sensitivity than when you included CIN 2. That is because CIN 2 has more interobserver variability on the histologic scale. There are a lot of problems with inflammatory immature metaplasia and differentiating that from CIN 2.

DR. WILSON: We have time for one more question.
Dr. Mirhashemi?

DR. MIRHASHEMI: This question is directed to Dr. Lorincz. In the six studies that you had mentioned, did they standardize the viral load and was that correlated with the sensitivities and positive predictive values?

DR. LORINCZ: In all of the studies that used the Hybrid Capture II test, the viral load at the cutoff was standardized to 1 picogram/ml. I would like to note here that, although the HPV test can be used in a semiquantitative manner and we can look at that data, we simply used a cutoff criterion, above 1 picogram/ml, positive, below that was negative.

In one of the studies, one of the Latin American studies, we actually compiled a combination of Hybrid

Capture I and Hybrid Capture II. The former Hybrid Capture test, which is no longer available, had a significantly lower sensitivity at 10 picograms/ml.

In the data that we presented, that is reflected by the fact that there is a lower sensitivity of the HPV test. If I recall correctly, it was about 84.3 percent that we presented and that was due to the fact that that was a combination. But that was the only study that was affected by that consideration.

DR. WILSON: Thank you.

We need to move on to our next speaker who is Dr. Mark Rosenfeld who is Vice President of Impact Diagnostics, Incorporated. Dr. Rosenfeld?

Impact Diagnostics, Inc.

DR. ROSENFELD: I am Dr. Mark Rosenfeld of Impact Diagnostics. I am joined today by other members of the company that, during any questions or comments, I would have these folks pitch in and answer. The members that will be doing so are Dr. Ron Torres, a member of our research group based at Utah State University, and also Dr. Dennis Hooper, who is our regulatory consultant.

Impact Diagnostics is a member of an increasing number of companies dedicated to producing products of increased sensitivity and specificity with respect to human papilloma virus. With respect to Impact Diagnostics, we are

currently pursuing an inexpensive, rapid and sensitive method for detecting HPV presence.

Our emphasis is on the detection of low-grade cervical disease. We are more at the nuclear stage than the folks at Digene. Digene did a wonderful job on coverage of the epidemiological evidence with respect to HPV having a strong link with cervical cancer. So, therefore, I am not going to beleaguer you with more epidemiology work in lieu of the time.

However, I do want to mention, because it was brought up during the question and answers, in which it was stated--something with regard to the fact that HPV types are mixed together in the Digene assay in support of mixing types, oncogenic types, of HPV. There is some literature on this now.

Oncogenic sorts of HPV seem to have an equal probability with respect to causing cervical disease. So, in that sense, the mixing and not typing to a specific viral type is actually an appropriate strategy.

What I want to do is actually cover a few items. I will not be giving much data at this stage of the game, but what I wish to do is to address the questions from the perspective of Impact Diagnostics and, also, apologize personally in the fact that I come from the research arena. I have never testified nor attended an FDA meeting, so I am

actually, to quote myself earlier, this is a black box to me. I am used to getting up and fighting and arguing.

In any case, the first question that had been proposed by the panel was what criteria should be developed to support the safety and effectiveness of HPV assays used in conjunction with Pap smears or without Pap smears for predicting risk for cervical cancer.

I have this divided into three comments. They cover safety, sampling and effectiveness. With regards to safety, I think that whatever we with regards to HPV testing has to be defined as being minimally invasive, preferentially utilizing established methodology. Another factor that I don't see touched on too, too often and that is that we have to minimize the level of discomfort and, in particular, embarrassment to the patient.

Pap smears, and we are not advocating from our perspective, the replacement of Paps by any means. However, people do find them quite discomfoting. For certain people, they are adequately embarrassed and, for certain social groups, they will not get these. This has to be taken into consideration with regard to the sampling.

At the same time, with regard to the sampling, we have to pay attention to specimen adequacy and accuracy.

In terms of establishing that, and this is something that can be discussed in question and answer,

especially with our regulatory consultant. In terms of assessing sampling methodology and safety, we feel that this may be designed around tests already established by the FDA. For example, the criteria that established the beta HGC urine test, if urine were to be used, would be the same criteria that we might want to establish with regards to the safety for an HPV test. Another example would be the strep swab, the fluorescent strep swab.

Effectiveness is a touchy issue from our perspective because, to me, at least, effectiveness means that it requires a definition, and that is effectiveness will be defined regarding the level of disease that will be detected. So, rather than saying we are effective, or someone else saying they are effective, guidance is going to be required by the panel or some entity with regards to the level of disease that one wishes to detect.

I also want to mention, because this is becoming something very active on the part of work that I am doing in Salt Lake City, and that is that Pap smears seem to be very inadequate with regards to adenocarcinomas meaning, in this case, that cytology seems to miss these at a fair frequency. In interviewing with various clinical laboratories that do Pap cytology, this seems to be a major topic.

I know, for example, that the interpretation of AGUS is quite controversial. In that sense, since there is

a link between human papilloma virus and adenocarcinoma that is quite strong, that HPV testing should be emphasized in the sense that it would allow us to get adenocarcinomas diagnosed earlier and at greater frequency than they are currently being done.

The next question I want to discuss is what would the appropriate interpretation of results from human papilloma virus assays be when used in conjunction with or without Pap smears. This has actually been touched on by the previous presentation. However, I do want to mention a few things.

One is that definitely--and this has been a major emphasis already today--and that is as an adjunctive test to Pap smears for primary screening. Perhaps that will help influence the effect on screening intervals.

I did not mention cost earlier, but a concern of mine--I tend to be cheap. What I mean by that is if you open up--in fact, when you go to the lobby, get your free copy of USA today. On the front page, they are now talking, again, as usual, about the rising cost of medical care and the rising cost of diagnostics and so on and so forth, and the big problems with regards to HMOs and so on and so forth.

One of the concerns that I have had for quite a long time, and part of the reason for my entering into the

medical industry, is that every time that one has increases in diagnostic capacity, it usually is accompanied by dramatically increased costs. This is something that, if we can absorb this into health planning, it allows us, for example, increase of screening intervals where we make up some of the costs.

Okay; that's great. But, on the other hand, if we can find other ways to do certain tasks, for example, in this case, human papilloma virus, then these are what should be emphasized. There is a study from Duke University that has actually looked into the cost-effectiveness of screening and they do question it.

I don't agree with them. On the other hand, they do question the increased cost and emphasize, from their perspective, that rather than HPV testing, there should be just increased emphasis on the application of Pap smears across the population.

Their model changes--if you look at the mathematical model used in that, that model changes if we can offer screening for HPV at a lower cost. So these are items that need to be considered.

Again, appropriate interpretation. Okay; we can use it as an adjunctive test. Also discussed earlier was that it could be used as a subsequent test for triage of women with equivocal or abnormal Pap smears. Discussed

already had been the fact that the presence of HPV, especially with an abnormal Pap smear, can suggest an underlying CIN 2 or 3 in which case we can now refer the patient to a colposcopy-directed biopsy.

I will only make this a very short and brief statement, and probably will raise the ire of my regulatory consultant, but, in any case, what hasn't been discussed here is that the human papilloma virus is actually linked to several other cancers. I am sure many of you, if not most of you, are aware of this.

With an appropriate test for human papilloma virus, it would allow the probing for cancers not readily detected via Pap smears; that is, in other parts of the body as well as cancers, female cancers, that are just not--for example, the adenocarcinoma, bulbar cancer and so on, that are not readily detected via Pap smears.

A primary concern that I have at this time is actually verification methodology; that is, given that one wants to look at new test, a new sampling technique, how do we go about this. What are our gold standards. There actually seems to be unclarity, for lack of a better word, with regard to this.

For example, if one uses blood, other body fluids, urine, et cetera, how do we evaluate this with regards to cervical cancer, in this case? What we propose for such

verification is that all assessments of novel or new collecting sources, or new techniques, be compared against, of course, the Pap. Again, I emphasize that we are not advocating at this time, and probably not for the very distant future, the replacement of the Pap but that this be evaluated with respect to the Pap, also for scientific verification, maybe not FDA verification, that there also be nucleic-acid detection. That can be defined as PCR. It can also be defined as Southern Blot. It can also be defined as DNA hybridization.

However, the gold standard for such tests we feel should be some biopsy methodology. However, I have concerns about Cone biopsies and subsequent problems that may befall certain women after a Cone biopsy. But, in any case, biopsy needs to be the standard so that we use an anatomical/cytological perspective and, on biopsy material, that this also be examined for HPV via another methodology.

We are considering right now peroxidase verification for such purposes.

I am going to actually stop my presentation at this stage. As I said, I did not want to inundate people with epidemiological work because you have had, actually, much of what I was going to say there. I thank you for the opportunity and my first appearance at the FDA.

DR. WILSON: Thank you. Do any of the panel

members have questions for Dr. Rosenfeld? Dr. Myers?

DR. MYERS: I guess, first of all, I should say that study that Dr. Rosenfeld cited was also funded by HCPR. Just for the record, I don't think characterization that it questioned screening for cervical cancer, per se, is accurate. The modality can certainly be questioned and debated.

But this is a question, a generic one. The point that Dr. Lorincz made earlier that a small increase in sensitivity may represent a large increase in the number of cases detected when the prevalence is high is true. A small decrease in specificity, given that the normal population is much, much larger than the abnormal population, means that there will be an even higher number of false-positive results.

Should that be a safety consideration for the panel to consider?

DR. HOOPER: My name is Dennis Hooper. I am and M.D., Ph.D., pathologist and microbiologist. To answer that question, I do think that should be considered. Decreased specificity is very important in looking at any kind of home-testing or in a clinical laboratory.

I also think that it would be very important in how are you going to correlate that result. If you are correlating any new tests, be it urine, plasma, serum or

even a swab, are you going to correlate it against the Pap which has a very low--well, low sensitivity and specificity, or are you going to correlate that against a tissue biopsy and possible further testing?

I don't know if that answers your question.

DR. MYERS: I think it is a question that will come up later in some of the discussions.

DR. HOOPER: Right.

DR. WILSON: Any additional questions? Thank you.

The last part of the presentation before the break is a statement from Dr. George Wendel who is going to state some information from the American College of Gynecologists and Obstetricians.

American College of Gynecologists and Obstetricians

(ACOG) Position

DR. WENDEL: Thank you. I would like to take this opportunity to summarize the American College of Obstetricians and Gynecologists position on cervical cancer screening and counseling. There are several types of publications that deal with this important topic, and I will briefly just mention the four that are the most germane to this discussion.

Two of them, actually, were just released this month and you may not have seen them. They are in the December issue of Obstetrics and Gynecology that just came

out. The first document is an ACOG committee opinion from the Committee on Gynecologic Practice, which is No. 246 from December of 2000 entitled, Primary and Preventive Care, Periodic Assessments.

These periodic assessments provide an excellent opportunity to counsel patients about preventive care. They are recommended yearly or as appropriate and should include screening and evaluation and counseling based on age and risk factors.

ACOG recommends pelvic examinations commence annually when sexual activity begins or by age 18. After age 18, annual Pap testing is recommended with patient and physician discretion after three consecutive normal tests in women who are considered at low risk.

The second document was also released this month and I believe it is in the packet for the panel members. That is Technical Bulletin No. 247 which is entitled Routine Cancer Screening. The document notes the effectiveness of Pap smear testing to diagnose preinvasive cervical lesions that, when treated, will result in a decreased incidence of invasive cancer and deaths from invasive cancer.

The document also importantly notes that 90 percent of women over age 18 in the United States have had at least one Pap smear and that over 60 percent of women in the United States have had a Pap smear within the last

three years.

They also note that considering that cervical cancer has not been eradicated, that the incidence of cervical interepithelial neoplasia seems to have increased over the past decade, that the Pap test has an appreciable false-negative rate, and that women tend to extend screening intervals from guidelines recommending annual cervical cytology, it seems prudent and warranted if early precursors to cervical cancer are to be detected and successfully treated, that these guidelines continue.

The third document is an ACOG Technical Bulletin No. 193 from June of 1994 entitled Genital HPV Infection. This document addressed many of the issues that we are discussing today and has been alluded to. ACOG stated that the role of HPV screening for cervical neoplasia is currently being studied and it is not currently recommended routinely.

The fourth document that has been mentioned several times is ACOG Committee Opinion No. 152 from 1995. This is entitled, Recommendations on the Screening Frequency of Pap-Test Screening. This document was in response to the American Cancer Society recommendation that three consecutive negative Pap tests may lead to less frequent Pap testing at intervals of up to three years in low-risk women.

This document did not deal with HPV testing at

all. The document cautions about the limitations of the recommendation due to the fact that Pap testing has a significant false-positive rate. There are failures of patients to return at regular intervals and that there is a difficulty in identifying women into high and low-risk categories for HPV infection.

Finally, the Gynecologic Practice Committee has addressed the issue of HPV screening several times, most recently at its May 2000 meeting. The committee reaffirmed the previously mentioned guidelines on HPV testing and Pap-smear testing intervals and awaits further results from ongoing prospective trials, as was mentioned, the ALTS study and the upcoming Bethesda meeting.

The committee also addressed the Digene product in May of 1998 and considers its use to currently be investigative. At this time, ACOG feels that as both an active participant and an observer on the important issues of HPV screening and cervical-cancer prevention, they are in a holding pattern currently and hope to readdress the issues and the exciting new technologies in the upcoming year.

Thank you.

DR. WILSON: Thank you.

Does anyone have any questions?

DR. BURK: Could you comment on the intended use of the Pap smear? I think we teach medical studies that,

really, it is not a single stand-alone test, given the sensitivity and specificity that it has, and that it is really meant to be used as a conjunction.

We always--or at least I learned in medical school, that three tests really was its intended use. This could have implications in cost-effectiveness and in whether one compares single testing versus multiple testing in the HPV-screening modalities or the Pap-smear modalities.

DR. WENDEL: Yes. I think your comment basically addressed your question, to me at least. The Pap smear really is a screening test to identify treatable lesions that are precursors for cervical cancer.

DR. BURK: But is it fair to use a stand-alone single Pap test? Is that its intended use?

DR. WENDEL: No; you are exactly right. It is used in conjunction with a whole host of other things along the algorithm of progression to repeat testing, colposcopy and then surgical intervention.

DR. WILSON: Any additional questions?

DR. DURACK: I think Dr. Burk was asking whether it is the stand-alone test or used with two other Pap tests. I just want to clarify that. Was that the--

DR. WENDEL: I am not sure I understand your question, then.

DR. BURK: In other words, in the use and the

specificity and sensitivity of the Pap test, I think it was recognized that a single Pap test is insufficient for completely--this is my own opinion--insufficient for adequate precancer or cancer screening of the cervix and that, really, one requires multiple Pap tests to adequately cover the population.

For us to adequately be sure that U.S. women are being screened adequately for cervical cancer, my impression, and maybe you could clarify this from the position of the College or your own professional opinion, that three tests were required to really cover the population and really substantially decrease their risk in the development of cervical cancer.

DR. WENDEL: Yes. I think, the ACOG documents speak to that difficulty, that it really isn't a single test, that it really should be part of an ongoing health-maintenance program and that it is difficult to classify people into the category of low risk.

I think the statement on the frequency of Pap-testing intervals was more of a caution, that ACOG recommends annual Pap testing in concert with a full examination and that it really should be the exception rather than the rule that patients would get three consecutive negative Pap smears and then go to more prolonged testing intervals because, when you look at what

are the low-risk categories, a decreasing percentage of patients actually fit in those. I think that is often lost in the details.

DR. MIRHASHEMI: Just a comment on that. I think we would all agree that the cervical milieu is a very dynamic organ and, as we know, as patients age, the transformation zone retracts back. So I think, because it is such a dynamic milieu, it is important to proceed with subsequent Pap tests. Probably one Pap test is not enough.

DR. WILSON: Let's go ahead and break now. We are a little bit behind the schedule. Let's reconvene at 11:20.

[Break.]

DR. WILSON: I would like to reconvene the meeting now moving to the Open Public Hearing. These will be a series of presentations given by individuals who have contacted the Executive Secretary prior to the meeting or anyone in attendance who will address the panel and present information relevant to today's issue.

I would like to remind each of the presenters that they need to state their financial or another involvement with HPV device manufacturers. I would like to ask the panel members to hold questions until after the series of presentations.

We are going to change the order of the presentation just slightly to accommodate one of the

speakers. The first speaker will be Dr. Willa Brown from the American Medical Women's Association, Director of Clinical Services for the Bureau of Nursing and the Howard County Health Department.

Open Public Hearing

DR. BROWN: Thank you. I am actually not in the Bureau of Nursing, but I am proud to have it on the schedule. The topic for the American Medical Women's Association is the need for consumers to have accurate information about the strength and limitations of current cervical-cancer screening protocols.

The American Medical Women's Association was founded in 1915 and is dedicated to promoting women's health and furthering the professional development and well-being of women in medicine. AMWA, the American Medical Women's Association, represents 10,000 women physicians and medical students dedicated to advancing women's health through advocacy and education.

AMWA commends the FDA for holding this hearing as it is evidence of its commitment to improving health and healthcare for women. AMWA supports women's access to comprehensive, accurate and affordable healthcare services. We believe that women have a responsibility to be actively involved in their healthcare and the medical community has the responsibility to fully inform women of their healthcare

options for diagnosis and treatment.

AMWA looks forward to the introduction of new options for screening and prevention of cervical cancer in the form of HPV testing. Women deserve access to the best detection methods available and increased effective healthcare options. AMWA is pleased to have the opportunity to provide input into the process by which further applications for the current test will be evaluated.

You will, no doubt, receive testimony on the safety and effectiveness of HPV testing. AMWA supports the use of HPV testing as an adjunct tool for triage of equivocal Pap smears. Women deserve access to the best and most accurate testing method available which can be determined using the existing data.

Full information about the test's adequacy should be provided to women so that they may make the most appropriate healthcare decisions for themselves and their families. As lead campaign partner for the National Cervical Cancer Public Education Campaign, AMWA is attempting to increase public awareness about cervical cancer. Every year, women die needlessly of cervical cancer as it is curable when detected early.

Financial and cultural factors play a role in women's health decision-making regarding HPV testing. Financial concerns are of particular significance to

healthcare consumer when medical regimens require additional unexpected visits to a provider. These visits often translate into increased time away from work and/or increased child-care needs.

Also, women who experience cultural barriers regarding pelvic exams are not likely to regularly request cervical-cancer screening. Every effort should be made to reach women who might not otherwise be screened and target the large numbers of women who experience cultural or economic barriers to the screening.

AMWA's goal is to enable women, through full and comprehensive education, to discuss cervical cancer and the importance of regular and effective screening with their healthcare provider.

In summary, AMWA supports the patient's right to have full knowledge of the link between HPV and cervical cancer. Also, women have the right to be fully informed about the best methods for detecting cervical cancer and the availability of effective treatment or precancer cervical disease and cervical cancer.

We need to adopt testing indications based on the best available data which eliminate cervical cancer as a cause of death. Women and their partners deserve no less.

Thank you.

DR. WILSON: Thank you, Dr. Brown.

The next presentation will be by Dr. Walter Kinney who is a gynecologic oncologist at Kaiser Permanente in Sacramento, an Associate Clinical Professor of OB-GYN at the University of California at Davis.

Dr. Kinney?

DR. KINNEY: Thank you.

[Slide.]

The opinions expressed this morning are my own and not those of the Permanente Medical Group, although it should be noted that I am the first author of the last two sets of cervical-cancer screening recommendations for our 3 million members.

As regards my relationships to industry, most of my funding for research has come from internal Kaiser money. However, I have received funding at different times from Digene, from Cytyk, from 3-M and from other industry sources. I also serve on the Speakers Bureau for Cytyk and Digene.

I want to talk to you today about the relationship between screening-test sensitivity and invasive cervical cancer.

[Slide.]

One of the folks who preceded me talked about various ACOG documents. This is the ACOG Today pamphlet that goes out to all of the fellows of ACOG from March of

1999.

[Slide.]

In it, we find the statement that a conventional Pap test, obtained as recommended on a regular basis, brings the chance of developing invasive cervical cancer almost to zero. This is a widely held view amongst experts. It is absolutely untrue, in my experience. Until we can move beyond this, we cannot make progress about cervical-cancer screening.

As has been pointed out, the sensitivity of convention Pap smears for histologic dysplasia is not very good. It is a little better than flipping a coin but not much. The traditional approach to that problem has been to repeat the test on a frequent basis.

[Slide.]

Unfortunately, that is not an adequate remedy. Conventional wisdom assumes that the sensitivity of each sequential screening test is independent of the previous screening test having occurred. This assumption is not valid.

Spoken in plain English, lesions that are difficult to detect on one cytologic screening test remain so on a subsequent Pap smear. IARC data are compatible with an 80 percent test sensitivity at the five-year interval, 60 percent at a two-year interval and 37 percent for annual

screening, and that assumes a six-year detectable preclinical phase if, in fact, the detectable preclinical phase is longer, then those numbers are even worse.

[Slide.]

The predictable consequence of that is that women who have been participating in this screening program do, in fact, get invasive cervical cancer. We got some internal Kaiser money to read the charts on everybody who has gotten invasive cervical cancer in our health plan on a seven-year period.

40 percent of those women had been participating in the screening program. This was published in Cancer in May. Nearly 30 percent had had one or more normal smears and no abnormal smears in the three years prior to their diagnosis. Now, you can look at this information and say, "Golly, you folks don't run a very good lab." And that is not, in fact, true.

[Slide.]

George Sawaya and David Grimes published this same information for the SEER population and that same 30 percent of cervical cancer occurring as a consequence of errors in sampling and interpretation was present.

[Slide.]

The practitioner's task, when they see someone in the clinic, is to exclude the presence of histologic high-

grade dysplasia or cancer and to define the interval to the next screening test which is, in large measure, a function of the risk that histologic high-grade dysplasia or cancer has been missed.

[Slide.]

Recognizing the extraordinarily compelling nature of the data that has been presented to this panel and other unpublished data as well, we believe that the negative predictive value of combined cytology and HPV testing helps with the definition of intervals, particularly in high-risk women.

In January of this year, it will become the recommendation of our group to use this combination for women in the following categories; follow up of untreated histologic LSIL, LSIL Pap smear and noncorrelating colposcopy histology, and in test of cure following LEEP.

[Slide.]

But intervals are much more important. This is 1986 British Journal of Medicine article from the International Agency on the Research on Cancer wherein they pooled data from ten sites and used case-control methodology to demonstrate that screening at one, two or three-year intervals in relation to no screening was very similar. However, the costs were dissimilar. This was replicated by David Eddy in the Annals of Internal Medicine who concluded,

for most women, a three-year frequency of screening is appropriate.

[Slide.]

To summarize, a wordy slide. Everybody believed him. We have moved to two- and three-year screening interval recommendations with virtually all major organizations, some with the benefit of multiple negatives prior to starting extended intervals.

[Slide.]

I have some reservations about how the IARC analysis was done and two of them that are fixable pertain to the fact that the intervals were defined in a way that don't reflect what clinically happens and, secondly, that the results were expressed as relative protection--that is, compared to no screening ever.

I respectfully submit to the panel that no screening ever is not a valid public-health alternative in the United States and, as a consequence, what we really should be doing is looking at the differences between one and two, and one and three, and two and three-year screening intervals.

[Slide.]

The interval definitions I mentioned have to do with this problem. This is unpublished information about 57,000 women who had a negative smear in early 1997 in our

regional lab and when they had their next smear. If you tell somebody to come back in a year, they don't all come back before twelve months. They come back in a peak around twelve months.

[Slide.]

The IARC defined their screening intervals as one-year being 0 to 12 and two years being 13 to 24, and so on.

[Slide.]

When we looked at this, we decided it would be much more reasonable to divide the intervals in ways that reflect what people actually do when they come back for screening.

[Slide.]

This is unpublished information that has been accepted for presentation this spring. There will be a manuscript going out in the next couple of weeks. This is a case-control study that has taken us five years from our membership, 482 cases, 934 controls matched for age, length of membership and race, much larger sample sizes than the IARC from their ten sites pooled.

The base case was one-year intervals instead of unscreened. Our odds ratio for two versus one year with conventional Pap was 1.72. Three years versus one year was double the risk. And three years versus two years, we couldn't discern a difference.

Results were unaffected by controlling for the number of previous negatives, two and three years or three and five years, or ever having had an abnormal Pap smear in the Kaiser system.

[Slide.]

There are really only two ways that you can plausibly study the relationship between screening intervals and screening tests and invasive cervical cancer. You can study them with case-control methods or you can study them with mathematical modeling. What you can't do is study them with prospective, randomized, controlled clinical trials. No IRB in the United States will let you do that trial with occurrence of invasive cancer or death from invasive cancer as an endpoint and no patient in their right mind would sign a consent written by our lawyers that had those in endpoints.

As a consequence, these are the two ways that you can possibly go about studying this. Evan Myers and his colleagues have done an exquisite job modeling this. Of interest is the fact that, on the top line with conventional Pap smears, it looks like the relative risk between annual Pap smears and two-year Pap smears is approximately three, and between annual Paps and three-year Paps is approximately five.

It didn't look quite that bad in our case-control,

but, clearly, there is a difference. In addition, it looks like, top right-hand box, annual Pap smears looks a lot like risk at two years if the false-negative rate decreases by 60 percent.

I believe that that is something that is accomplishable with the technology that is presently available by a variety of modalities. Note that this is not a commercial for any particular vendor or any particular technique. What I am telling you is that there is clear utility in terms of outcome of invasive cancer to better testing.

[Slide.]

What we have been told up to this point is that test performance and cancer are completely unrelated. All you have to do is do conventional Pap smears on every women and cancer will go away. The test performance relates to expense and to the number of minimally abnormal and to the intervals, but it doesn't really have to do with cancer rates. In point of fact, that is really not true.

[Slide.]

It is all the same problem. Test performance is intimately related to cancer rates because, if you don't deal with intervals and minimally abnormal in a way that preserves access and produces resources enough to pay for better testing and chase the underscreened around, you

can't, in fact, change cancer rates.

I believe that what will happen is we will not move back to one-year testing intervals but we will, instead, go to better testing at longer intervals. I believe that is most likely to decrease cancer rates and to be respectful of the physician's and the patient's time.

That is the message I want to leave you with. Thank you for your attention.

DR. WILSON: Thank you, Dr. Kinney.

The next presentation will be by Dr. Linda Alexander who is the President and CEO of the American Social Health Association. Dr. Alexander?

DR. ALEXANDER: Good morning. I, personally, have no financial interest in any of the companies today. My organization receives its funding primarily from federal and state contracts, contracts with national health foundations, individual donations and some industry contributions of which Digene has been an occasional player.

Thank you for the opportunity to represent the voices of American women about the important health issue of HPV and cervical-cancer screening and testing. I am Linda Alexander and I am President of the American Social Health Association, ASHA.

I am a women's health educator. ASHA is an eight-six-year-old national nonprofit health organization

dedicated to addressing the spectrum of issues associated with all sexually transmitted diseases. Every day, ASHA interacts directly with nearly 15,000 individuals via our six major hot-line services, web sites and publications.

For nearly twenty years, we have dedicated outreach programs specifically for human papilloma virus. These programs include a national infrastructure of dedicated support groups, publications, advocacy efforts, hot lines and web sites.

Two years ago, we established the National HPV and Cervical Cancer Prevention Resource Center to centralize these efforts and provide national leadership and public awareness, patient education, provider training and public policy. Our programs are developed, implemented and evaluated with the assistance and oversight of a national advisory panel of esteemed clinicians, academics and women's health experts. Dr. Tom Cox serves as a dedicated and hard-working Executive Medical Director of the Resource Center.

My comments today will reflect the insights and the lessons learned from our interactions over the years with women throughout the nation. Today, you, the advisory panel, will hear many perspectives and opinions related to the use of HPV testing for general-population cervical-cancer screening.

Discussions and deliberations will focus on

evolving technologies and the challenges and opportunities that they present in cervical-cancer detection. Clearly, care and caution must be exercised with all technological and therapeutic advancements.

My comments will not address the complex issues of HPV or Pap technological achievements or imperfections. I will begin, however, by noting the topic before us today is a paramount women's health issue. The successes of the Pap test in our institutionalized gynecological infrastructure have probably saved millions of lives. But our current success is far from perfect.

Women have been taught that an annual pelvic examination is an important part of their routine healthcare. They now expect to be Papped on a frequent basis. Unfortunately, there are costs and down sides to the current process. The Pap test has limitations. A negative test does not always mean that the woman is free of cervical cancer and a positive test does not mean that she has cancer.

A woman with an abnormal pap may have to live with constant anxiety and fear of cervical cancer in between repeat testing or she may have to undergo repetitive and sometimes mutilative procedures for reassurance that she is cancer-free.

In spite of years of testing, women remain

confused about just what is a Pap test. Many women believe that a Pap test is highly reliable and others believe that it is a universal test for whatever could go wrong "down there."

Through our outreach efforts, we daily encounter women who believe that when they have a Pap test, they are being checked for infections. Others believe that, while a clinician is looking when doing a pelvic examination, that they are also being checked for sexually transmitted diseases. Clearly we, as clinical educators, have failed many in our education about the reality of pelvic examination and the Pap test. Our simplistic reassurances and guidance have unfortunate consequences.

The question has been raised whether testing women for HPV will create more anxiety than it is worth. Before discussing our response to this question, I would like to share the typical response when a woman learns about HPV and that a sexually transmitted virus causes cervical cancer.

The first response is almost universally anger and frustration. The anger is complex and often is directed in the difficult and impossible direction of "who gave this to me and when?" When we work through this challenge by acknowledging that we don't know and we probably will never know, the anger resurfaces, this time with the question, "Why wasn't I told?"

With accompanying frustration, the information has been intentionally withheld. Ironically, this perceived conspiracy of silence actually serves to further stigmatize the infection inadvertently sending the message that HPV is simply too awful to talk about.

So the ASHA response to the question of whether testing women for HPV will create more anxiety is no. Instead, HPV testing will ultimately thwart anxiety. Anxiety, in many forms, dominates the current arena of cervical-cancer screening. With the new paradigm of HPV testing, women can move from Pap to Pap-plus-HPV with the reassurance that a negative finding is truly negative.

This is important both for routine screening and for documenting and clearing HPV infections. Women will have a better understanding of not only HPV and the role it plays in causing cervical cancer but they will also understand that the Pap is not a universal diagnostic for reproductive-tract infections.

As a women's health educator, I am intrigued with the lessons that we can learn from the women's health movement. It was only a few decades ago that Margaret Sanger had to battle both politicians and clinicians to offer women education and protection for unwanted pregnancy.

In the early 1960's, we heard arguments that oral contraceptives were too complicated for women to take. A

few years later, we heard that home-pregnancy test results would drive despondent pregnant females off bridges and apartment buildings, and we listened to arguments that women could not possibly manage to self-diagnose repeat yeast infections and treat themselves with over-the-counter preparations.

Perhaps reflecting on these experiences can provide insight into the arguments that we are making today about HPV testing. I would submit that, as clinicians and educators, we owe women the option of understanding themselves, their risk and the technologies available today.

If we choose to hide behind a cloak of protecting women by withholding information, we will be adding yet another chapter in the book of therapeutic disservice to women. I urge you today to consider in your deliberations what women want. They want to know about themselves. They want to make informed health choices. They want to protect themselves, their partners and their children.

They want access to the latest health technology. They want to trust their providers and they trust that they are being told the truth. I urge you today to also consider in your deliberations what women can do. They can learn about themselves and about viruses that cause cancer. They can work through the angst associated with knowing that they acquired a virus through sexual relations.

They can make informed decisions about testing. They can urge their sisters and their daughters to be tested. But, to do these things, we, the healthcare community, must make the information available to them and offer them the options for informed decision-making.

Globally, cervical cancer is the second leading cause of death among reproductive-aged women. The world is watching today to see how we proceed with what we offer women with information and choice. Consider, please, that your decisions about HPV testing will have impact throughout the world.

We look forward to the day when cervical cancer no longer kills and stigma no longer accompanies an HPV infection. Please remember women everywhere as you proceed with your deliberations.

Thank you.

DR. WILSON: Thank you, Dr. Alexander.

The next presentation will be by Dr. Diane McGrory who is the Chief of Gynecology and Dedham Medical Associates in Wellesley, Massachusetts.

DR. McGRORY: Good afternoon. I want to thank the board for allowing me to speak today. I am really excited to be here because this could be a great day for women's healthcare.

This is one of my areas of interest since my

undergraduate days at Smith College when I had the opportunity to do virology research at the Harvard School of Public Health. I also must say that I have served on the speakers panel and advisory panels for the Digene Company. Right now, I am Chief of Gynecology at Dedham Medical Associates which is a multispecialty group practice in Dedham, Massachusetts. We serve 30,000 patients and we perform about 18,000 Pap smears annually.

In general, we have a well-screened population. Some of our patients fall out of screening for a few years but then usually return, so we would call them partially screened. This screening involves a yearly Pap smear and pelvic examination and we use both the traditional Pap smear and the liquid Pap smear.

We use reflex testing with Hybrid Capture II technology for the evaluation of the atypical Pap smear. We find it helpful to identify the patients with the precursor lesions and to help us get those women into treatment and to follow up. Our ASCUS rate is approximately 2 percent and we see about 38 percent incidence of HPV in that group.

92 percent of our Pap smears are normal and we would like to use HPV testing to further modify our screening program. In Massachusetts, a state of 6 million people, the state cancer registry records approximately 330 cases of cervical cancer per year.

The highest incidence of cervical cancer is in women over 45 and, actually, in our state, the highest incidence of cervical cancer is in women over 65. We see approximately 21 cases of cervical cancer per 100,000 women per year in the over-65-year population.

In Dedham Medical Associates, we have a fairly low incidence of cervical cancer as evidenced by a recent survey that we conducted of our 10 OB-GYN physicians. We have approximately 100 physicians in our practice, and internal-medicine physicians and pediatricians also perform Pap smears.

So this could be a little bit limited in the fact that an internist could possibly send out a cervical cancer without referring within our OB-GYN Department, so we could have missed a few cases. Over an eleven-year period, we have had thirteen cases of cervical cancer.

Who are these women? Our cervical cancer patients were actually younger than the state average age. We found seven women were between the age of 24 and 36 years of age. Eight patients were screened for several years with Pap smears and developed cancer.

Six women had no history of an abnormal Pap smear. Three women had fallen out of the system for three to five years and then presented with cervical cancer. Two women were not in our system prior to their presenting with the

cervical cancer.

So I wanted to make a little bit more of a clinical presentation for you so I will present two cases of this group. One case involves a 31-year-old woman with a high-grade SIL and carcinoma in situ, treated five years previous to her prescription with cervical cancer. She had been treated with a Cone biopsy that had margins that showed they were free of disease and she had multiple follow-up visits and subsequent Pap smears that were normal.

Then she presented to her gynecologist complaining of pelvic pain. A Pap smear was done and was normal. Subsequently, the workup for pelvic pain led to a biopsy a month later which showed invasive cancer.

Case 2 involves a 36-year-old woman who was a gravida 2, para 2, with a history of cervical dysplasia treated in her twenties with cryotherapy. Multiple follow-up Pap smears were normal and she complained at her yearly examination of some recent post-coital spotting. Her Pap smear was done and was normal, but the physician felt that the cervix looked a little abnormal and did a biopsy which showed invasive cancer.

The traditional American screening program failed these women. They did develop cancer. They were in the program and were what we call a well-screened program. We need to accept HPV screening as part of the overall

healthcare of American women. How the FDA and the Board treat HPV testing could be the "shot heard the world" for prevention of cervical cancer.

Our goal should be prevention of cervical cancer and, therefore, we need to identify the precursor lesions. We need to identify the women who are truly at risk for cervical cancer. Women have a right to be tested for HPV and they want to be tested as evidenced by a recent survey in our department of 112 consecutive gynecology patients. The age ranged 15 to 87 years of age.

73 percent were not aware of the link between HPV and cervical cancer. 85 percent of the patients stated that they would want to know if they carried a virus that caused cervical cancer. Better screening for all women should be our goal. For physicians to change their approach, they must first accept that cervical cancer has an infectious etiology.

This is not what we were taught in medical school. We were taught that it was associated with sexually transmitted diseases but, at that point, when I was in training, we did not discuss that HPV was the cause of cervical cancer.

Then we can move closer to the truth. We now have many studies in the literature which demonstrate the greater sensitivity of HPV testing over the traditional Pap smear

and women have the right to be offered this more sensitive test.

Thank you.

DR. WILSON: Thank you, Dr. McGrory.

Our next presentation, we invite Dr. Jerome Belinson, gynecologic oncologist in the Cleveland Clinic Foundation in Cleveland.

DR. BELINSON: I am happy to be here this morning to participate.

[Slide.]

This particular study that I am going to be discussing was funded by private donations to the Cancer Center, the Cleveland Clinic Foundation. It was funded also in services and supplies by Digene Corporation, Cytyk, Zeiss Corporation and Optical Biopsy, among others.

I am a gynecologic oncologist at the Cleveland Clinic. I have served as Chairman of the Department of Gynecology and Obstetrics for ten years. The Shanxi Province Cervical Cancer Screening Study is a cross-sectional comparative trial of multiple techniques to detect cervical intraepithelial neoplasia.

[Slide.]

If you look at the subject characteristics, the patients we screened were between the ages of 35 and 45 with a mean age of 39.1. This obviously was done in keeping with

world health organizations that, when you are developing technologies in third-world countries, it is most advantageous to begin screening at age 35.

[Slide.]

This is a somewhat complicated slide, but if you sort of move down to the center, there, this lists the technologies that were done; HPV self-test, fluorescent spectroscopy, use of Thin Prep for a Pap smear from which was done the HPV direct test. We did manual reading on the day the test was done far prior to when any biopsies were processed. Also autopap reading and also visual inspection.

[Slide.]

The hallmark of the study was that every single patient underwent colposcopy and, because we used a special virtually painless biopsy instruments, every single patient had a minimum of five biopsies that included all abnormal areas found on colposcopy as well as a biopsy of the squamocolumnar junction on every patient who had a negative quadrant from each of those quadrants as well as an endocervical curettage.

So what I supply for you is true specificity and sensitivity. This was really our goal because we figured if we were going to develop screening systems, we had to be dealing with reality.

[Slide.]

I show you this which, if we just focus on these two numbers here which says that the sensitivity for the Thin Prep pap was 94 percent and the specificity 78 percent. This is, obviously, very high. I think that it is high for several reasons. One, we had major expert cytology. Second, they were specifically trained on the technology that they were using. Third, it was almost like a medical-legal review because the incidence of abnormal disease was so high that they really expected abnormalities to be coming through about every fourth or fifth Pap smear.

[Slide.]

If you look at the performance, however, the direct test for HPV, it shows a sensitivity of 95 percent and a specificity of 85 percent. This is ultraconservative. We interpret this on the basis of results obtained, not tests done, because we were looking at it in a screening mode.

If you do it on the basis of tests done, the sensitivity is actually 98 percent.

[Slide.]

What did this really accomplish for us in terms of positive and negative predictive value? If you do a negative test, and we have these data, obviously, because the patients were biopsied--if you have a negative Pap smear, the negative predictive value was 99.7 percent.

[Slide.]

If you had an HPV test to that, a positive HPV test to a negative Pap smear gives you a positive predictive value of 3 percent and a negative predictive value for a negative HPV test of 100 percent.

[Slide.]

If you look at just the group, the patients who had an ASCUS Pap smear, the ASCUS Pap smear had a positive predictive value of 2.1 percent. If you add HPV testing to that, a positive HPV test had a positive predictive value, along with an ASCUS Pap smear, of 9 percent

Most importantly, instead of 290 patients who needed management, 53 patients would have needed management. A negative HPV test added to that ASCUS Pap smear result had a negative predictive value virtually the same as a negative Pap smear, 99.6 percent.

[Slide.]

The conventional use of abnormality as greater than or equal to ASCUS on a Pap smear, the positive predictive value--and I should say all these positive predictive values are for high-grade disease greater than or equal to SIL2--was 16 percent. When you add HPV testing to that, the positive predictive value goes to 38 percent and the number of patients who need management dropped from 506 down to 205.

Again, the negative predictive value for a negative HPV test with this group of women was 99.3 percent. I think this population from rural China, although they had a very incidence of preinvasive disease and cervical cancer, is certainly genetically related to the Asian women in this country. Therefore, I think data such as these are quite relevant.

[Slide.]

However, at the end of the day, I take off my clinical-research hat and I do what I was formerly trained to do and that is to take care of the women that I care for. I think often about what are the principles of management beyond the abnormal Pap test?

The HPV test allows me to help my patients understand that the goal of the Pap smear is to prevent cervix cancer. Our goal is not the create the perfect Pap smear but to prevent cervix cancer. The HPV test helps me identify real disease. As the former speaker pointed out, it certainly helps me educate my patients and not frighten them.

It supplies me with information that I can discuss with them and make them understand and help them understand the management of their disease and all the options that are available to them.

Thank you very much.

DR. WILSON: Thank you, Dr. Belinson.

Our next presentation will be by Ms. Phyllis Greenberger who is the Executive Director of the Society for Women's Health Research in Washington

MR. GREENBERGER: Good afternoon and thank you very much for the opportunity to express the views of the Society for Women's Health Research before you today. I would like to say, before I begin, that we have worked with Digene on public-education campaigns about cervical cancer and they are a member of our Corporate Advisory Council along with fifty other corporations that do research in women's health.

The primary topic of today's meeting, issues concerning the types of information necessary to determine the effectiveness of in vitro diagnostic devices that detect the human papilloma virus in women 30 years of age and older is of great interest to the Society.

The Society for Women's Health Research was founded in 1990 by researchers and activists seeking to address and end inequities in medical research. Our three strategic priorities are to promote the study and acceptance of sex-based biology in the scientific community, to enhance the recruitment and retention of women in clinical trials and to increase research funding for women's health research.

This society works to increase support for research on conditions that affect women solely, predominantly or differently from men. This, of course, includes diseases specific to women such as cervical cancer. We have watched with interest the great strides made in understanding the role of HPV and the cause of cervical cancer and the improvements in detection of cancer-related strains of human papilloma virus.

We now know that these oncogenic strains of HPV are found in 99.9 percent of all cervical cancers and we have a very good understanding of the natural history of the disease. Thus, we have the scientific framework to eliminate this cancer that today unnecessarily takes the lives of 5,000 American women.

According to available data, as many as half of these women likely tested negative for evidence of the disease using the traditional screening test, the Pap smear, in the three years preceding their diagnosis.

As we all know, the Pap smear has been used for primary screening for cervical cancer since its introduction over 50 years ago. But there are problems with the accuracy of the Pap smear and we now have the ability to add a second test for the presence of the cancer-causing strains of HPV. Current data suggest that in women over 30, combining HPV testing with Pap testing could increase the accuracy of

cervical cancer screening up to 98 percent.

These data were collected outside the United States. We understand that the FDA wishes to determine if non-U.S. data is sufficient and appropriate for U.S. regulatory considerations involving the use of HPV testing in conjunction with the Pap smear for women over 30 and older as a primary screening regimen for heightened risk of cervical cancer.

We would argue that it is appropriate for non-U.S. data from well-designed clinical studies to serve as the basis for FDA considerations. More and more clinical trials are being conducted outside of the United States for a variety of reasons. The FDA must recognize the reality of this trend and fully consider data from well-designed studies regardless of where the studies are performed provided, as in this case, that the study results are applicable to women in the United States.

Society also wishes to go on record in support of actions that make the best possible screening regimens available to women as quickly as possible. In this instance, it seems that there are two significant benefits from combining the Pap smear and HPV tests for primary screening.

First, when the Pap smear and the HPV test are used in combination, it is likely that cervical cancer will

be detected earlier and more accurately leading to a reduction in both morbidity and mortality. Equally important is the fact that women who test negative by both the Pap and the HPV test can be assured that they are not at risk of developing cervical cancer and can, therefore, have their screening interval extended and still enjoy peace of mind.

In conclusion, the Society wishes to commend the FDA for convening this public forum to discuss a question of great importance to women's health. We feel that there are sufficient data to assess the effectiveness of combination screening and we urge that a decision be made as quickly as possible.

Thank you for your attention.

DR. WILSON: Thank you, Ms. Greenberger.

The next presentation will be by Ms. Donna Richmond who is the Vice President of the Association of Reproductive Health Professionals, also in Washington.

Ms. Richmond.

MS. RICHMOND: Good afternoon. I thank you for this opportunity to share these brief comments with you. The Association of Reproductive Health Professionals, or ARHP, is an interdisciplinary association composed of professionals who provide reproductive health services or education, conduct reproductive-health research or influence

reproductive-health policy.

ARHP, founded in 1963, has a mission to educate healthcare professionals, public-policy makers and the public. The organization fosters research and advocacy to promote reproductive health. ARHP, as a non-profit, educational organization, firmly abides by national accreditation guidelines for identify support by producing credible and independent enduring materials for clinicians and consumers.

In 1999, we received funding in the form of an unrestricted educational grant from the Digene Corporation to develop a clinical monograph. Funding was not provided for participation in this review.

This statement is written to express our support for a woman's right to quality health education regarding the human papilloma virus, or HPV, its relationship to cervical cancer and the safe and effective options available for diagnosis and treatment. We recognize the important goal of improving screening and diagnosis of HPV to reduce the unacceptably high rates of cervical cancer in the United States.

To meet these needs, we strongly encourage all efforts to make as many safe and effectiveness diagnostic methods available to women as possible. It is understood that HPV is not a new emerging virus. However, almost all

of our understanding of the natural history and epidemiology of this group of viruses has only come about in the last twenty years with the advent of sensitive molecular tests that facilitate a description of the more than 100 HPV types now identified.

We now understand that genital infection with HPV is the most common sexually transmitted viral infection and that this virus manifests as more than just benign warts but has the capability for oncogenesis.

With this wealth of information as the basis for educating women and their partners, we firmly support clinical studies for establishing the safety and effectiveness of diagnostic options for human papilloma virus. This will be a positive step for women who have the right to accurate and reliable HPV detection.

Thank you.

DR. WILSON: Thank you, Ms. Richmond.

Our next presentation will be by Dr. Thomas Wright who is an Associate Professor of Pathology from Columbia University in New York City.

DR. WRIGHT: Good morning. I'm Tom Wright, a gynecological pathologist from Columbia University. I am the PI on a small grant by Digene to Columbia University and also serve on their Speakers Bureau.

I would like to thank the FDA for opening a