

SUMMARY MINUTES

OF THE

MICROBIOLOGY DEVICES

PANEL MEETING

OPEN SESSION

December 8, 2000

Gaithersburg Marriott
Gaithersburg, MD

Attendees

Microbiology Devices Advisory Panel Meeting December 8, 2000

Microbiology Devices Panel

Michael L. Wilson, M.D., Chair
Denver Health Medical Center

Margaret R. Hammerschlag, M.D.
State University of NY Health Science Center at Brooklyn

Carmelita U. Tuazon, M.D.
George Washington University Hospital

Melvin P. Weinstein, M.D.
Robert Wood Johnson Medical School

David T. Durack, M.D., Ph.D., Industry Representative
Becton Dickinson Biosciences

Stanley M. Reynolds, Consumer Representative
Bureau of Laboratories
Pennsylvania Department of Health

Panel Consultants

Donald A. Berry, Ph.D.
Department of Biostatistics
M.D. Anderson Cancer Center

Carol L. Brown, M.D.
Gynecologic Service
Memorial Sloan-Kettering Center

Robert D. Burk, M.D.
Epidemiology and Social Medicine
Albert Einstein College of Medicine

Juan C. Felix, M.D.
Surgical Pathology
Los Angeles County Women's and Children's Hospital

L. Barth Reller, M.D.
Clinical Microbiology
Duke University Medical Center

Guests

Laura A. Koutsky, Ph.D.
University of Washington
HPV Research Group

Evan R. Myers, M.D., MPH
Department of Obstetrics and Gynecology
Duke University Medical Center

Ramin Mirhashemi, M.D.
Division of Gynecologic Oncology
University of Miami School of Medicine

Guest Speaker

George D. Wendel, Jr., M.D.
Obstetrics and Gynecology
University of Texas South Western Medical Center
(Representing the American College of Obstetricians and Gynecologists)

FDA Personnel

Steven I. Gutman, M.D., M.B.A.
Director, Division of Clinical Laboratory Devices

Freddie Poole
Panel Executive Secretary

Thomas E. Simms
Biologist
Microbiology Devices Branch

Kristen Meier, Ph.D.
Mathematical Statistician
Division of Biostatistics

Marina V. Kondratovich, Ph.D.
Mathematical Statistician
Division of Biostatistics

OPEN SESSION—December 8, 2000

Panel Chair **Michael L. Wilson, M.D.**, called the meeting of the Microbiology Devices Panel to order at 9:38 a.m. and asked the panel members to introduce themselves. The Executive Secretary, **Freddie Poole**, read the conflict of interest statement, noting that matters involving **Robert D. Burk, M.D.**, and guest **Evan R. Myers, M.D., MPH** had been considered and waivers granted to allow their full participation. **Dr. Wilson** then stated that the charge to the panel was to discuss the appropriate types of information necessary to determine the effectiveness of in vitro diagnostic devices that detect human papilloma virus (HPV) 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 was to discuss and make recommendations on issues concerning the use of HPV devices without Pap smear to determine a woman's risk of cervical cancer, as well as the use of self-collection and alternative specimen sources.

Opening Statement

Steven I. Gutman, M.D., M.B.A., Director of the Division of Clinical Laboratory Devices, stated that the day's discussion would provide an opportunity to help the Food and Drug Administration (FDA) and industry sponsors develop clear and less burdensome pathways for certain types of assay devices seeking regulatory approval. He observed that there are few tests as important in public health consequences as the Pap test for cervical cancer, and that the FDA was interested in the potential of new tests, with or without the Pap smear, for cervical cancer and in obtaining panel advice on expansion

of datasets, future testing directions, data thresholds, and labeling requirements for such devices.

Industry Perspectives on Issues

Mark Del Vecchio, Director of Regulatory and Clinical Affairs for Digene Corporation provided an introduction to the Digene Hybrid Capture High-Risk HPV DNA test and introduced the Digene presenters.

Attila Lorincz, Ph.D., Senior Vice President and Chief Scientific Officer of Digene, presented information on the role of HPV screening in the diagnosis of cervical disease and summarized HPV infection pathways and the role of high-risk HPV subtypes in carcinogenesis. Dr. Lorincz presented findings from three U.S. studies on ASCUS triage, as well as the results of a prospective study in Oregon on natural history of HPV infection. He also cited six studies on foreign HPV screening trials from which Digene concluded that the sensitivity and negative predictive value of HPV testing are always greater than the Pap smear alone and that HPV plus Pap testing further improves sensitivity and negative predictive value over Pap testing alone. Dr. Lorincz discussed applicability of the foreign data to the U.S. population, and cited conclusions of a WHO/EUROGIN April 2000 meeting.

J. Thomas Cox, M.D., consultant for Digene and Director of the Gynecology and Colposcopy Clinic at the University of California, presented his opinions on cervical cytology screening (Pap testing) and the problems with cytology, i.e., high interobserver variability, misclassification of results (particularly in older women), equivocal results,

false negatives, and poor patient compliance. He noted that HPV testing could clarify these results and suggested a diagnostic algorithm for women 30 years of age and above.

Mark Del Vecchio described currently approved claims for the Digene Hybrid Capture High-Risk HPV DNA test and read a proposed expanded indication for use, along with ways the firm proposed to submit information to the FDA to support this indication. He concluded by addressing the FDA questions posed to the panel and provided the firm's analysis of criteria required to support the safety and effectiveness of HPV assays. He presented what Digene believes was an appropriate interpretation of results from HPV assays with Pap testing in women 30 years of age or older and information required to establish safety and effectiveness of HPV testing to determine risk for cervical cancer in a U.S. population of women 30 years of age or older. The panel questioned the firm about the recommended interval for testing and the specificity of HPV and Pap smear testing.

Mark J. Rosenfeld, Ph.D., Vice President of Impact Diagnostics, Inc., provided his perspective on the shortfalls of the Pap test and HPV testing as an adjunct to Pap smear for triaging of patients. He also addressed the FDA questions to the panel. He believed that criteria for specimen adequacy and accuracy have already been established by the FDA for assays such as *Streptococcus* and beta HCG urine testing, and similar criteria could be developed for HPV. He stated that HPV testing should be used as an adjunctive test to the Pap for primary screening, which would lower cost and improve the interval between tests, and for patient triage for those with abnormal Pap smears. He emphasized the importance of verification by comparison to a gold standard, which should be some biopsy methodology from a cytological perspective.

American College of Gynecologists and Obstetricians (ACOG) Position

George Wendel, Jr., M.D., of the University of Texas SouthWestern Medical Center, summarized ACOG's position on cervical cancer screening and counseling. He cited four ACOG publications on frequency of gynecological testing, routine cervical cancer screening, screening for HPV infection, and recommendations on screening frequency of Pap testing, which made no recommendation on HPV testing but reaffirmed the annual guidance on Pap testing every three years after three consecutive normal Pap tests. He stated that ACOG considers the Digene assays to be investigative tests (for changing current medical practice), and is currently awaiting results of the ALTS trial and the Bethesda meeting and will soon assess its position on HPV testing.

OPEN PUBLIC HEARING

Dr. Wilson opened the meeting to persons who had previously contacted the FDA. There was a change in the agenda to accommodate a speaker. The other speakers agreed.

Willa Brown, M.D., M.P.H., spoke on behalf of the American Medical Women's Association, Inc. (AMWA), and disclosed that 1% of their annual budget included funding from Digene Corp. She stated that AMWA supported the use of HPV testing as an adjunct tool for triaging patients with equivocal Pap tests. She further stated that AMWA supported the patient's right to have full knowledge of the link between HPV and cervical cancer and to be fully informed about the best tests for detecting cervical cancer and the availability of effective treatment for precancerous cervical disease and

cervical cancer. She stated that testing indications should be adopted based on the best available data in order to eliminate cervical cancer as a cause of death and that women deserve no less.

Walter Kinney, M.D., Gynecologist/Oncologist of Kaiser Permanente, Sacramento, disclosed that his views were not representative of Kaiser Permanente, and he had received funding from Digene Corporation, Cytoc, and 3M Corporation. He presented information on the relationship between screening test sensitivity of annual Pap smears and invasive cervical cancer. He referenced the SEER population study, which showed that up to 30% of cervical cancer cases were missed because of sampling and interpretive errors. Dr. Kinney concluded that one-year HPV and Pap testing intervals would produce the desired combination of decreased cancer rates and improved test performance.

Linda L. Alexander, Ph.D., spoke on behalf of the American Social Health Association (ASHA) disclosed that they received funding from Digene and provided ASHA's perspectives on HPV and cervical cancer screening. She noted that the Pap test has probably saved millions of lives, but is far from perfect in screening for cancer and has also been misunderstood as a universal diagnostic for reproductive tract infections. She asked the panel to consider women's needs to make informed health choices, to protect themselves and loved ones, and to have access to the latest health technology. She urged the health care community to make information available to women and offer options for informed decision-making.

Diane McGrory, M.D., Chief of Gynecology Oncology at Dedham Medical Associates, disclosed that she had served as a consultant for Digene. She presented two

case studies of women from a well-screened population (annual Pap testing) who developed undetected invasive cervical cancer. Dr. McGrory concluded that many studies in the literature demonstrate the greater sensitivity of HPV testing over the traditional Pap smear.

Jerome Bellinson, M.D., of the Cleveland Clinic Foundation spoke on the true sensitivity and specificity of HPV in an unscreened population. He presented results from a cross-sectional comparative trial of multiple techniques to detect intra-epithelial neoplasia, the Shanxi Province Cervical Cancer Screening Study. He described study characteristics, study protocol, and results, which showed high sensitivity and specificity for the HPV test and a high negative predictive value, especially when combined with the Pap test. Dr. Bellinson stated that the HPV test helps focus on preventing cervical cancer, identifying real disease, and educating rather than frightening women.

Phyllis Greenberger, executive director of the Society of Women's Health Research, affirmed the Society's support for non-U.S. data from well-designed clinical studies to serve as the basis for FDA considerations and for making the best possible screening regimens available to women as quickly as possible. She stated that there are two significant benefits from combining the Pap smear and HPV test for primary screening: to detect cervical cancer earlier and more accurately, leading to a reduction in morbidity and mortality, and assuring those who test negative that they are not at risk of developing cervical cancer and can have their screening interval extended. The Society feels that there are sufficient data to assess the effectiveness of combination screening and urges that a decision be made as quickly as possible.

Donna Richmond, BSN, MPH, spoke on behalf of the Association of Reproductive Health Professionals on women's right to health education regarding HPV and its relationship to cervical cancer. She stated that the Association recognized the important goal of improving screening and diagnosis of HPV to reduce the unacceptably high rates of cervical cancer in the United States. Noting the advances in knowledge about HPV and its capability for oncogenesis, the Association supports clinical studies for establishing safety and effectiveness of diagnostic options for HPV.

Thomas C. Wright, Jr., M.D., of Columbia University spoke on results of HPV DNA screening trials in South Africa, noting that Dr. Lorincz had already discussed findings from that study in his earlier remarks. He discussed the applicability of results to U.S. populations and the reason for high prevalence of HPV in the Cape Town screening study. He summarized the potential advantages of HPV testing as greater sensitivity than cytology, potential to increase screening coverage through self-collected specimens, and the ability to inform women of their risk. He presented incidence rates of cervical cancer in New York in various racial and ethnic groups, noting the lower screening rates in older and poorer women that often result in high cancer rates in black and Hispanic populations. He strongly supported the approval of HPV DNA testing for high-risk subtypes as a primary method of cervical cancer screening in women 30 years and older in the United States.

The Executive Secretary read excerpts from a letter from **James Linder, M.D.**, of the University of Nebraska Medical Center, and a consultant to Cytoc Corporation, the manufacturer of the ThinPrep Pap test, in which he supported HPV testing as an adjunct to morphologic cytology and said he believed the role for HPV detection assays or other

molecular markers will grow. He warned that using the conventional Pap smear as a measure of HPV test sensitivity might not be appropriate, considering the smear's lower sensitivity as compared to the ThinPrep method. He suggested that if HPV testing were used as a screening adjunct, as opposed to reflex testing of ASCUS Paps, the HPV testing platform would have to have specificity for the recognized HPV high risk subtypes to prevent false positives. He encouraged the panel to engage professional organizations representing pathologists, gynecologists, as well as groups within FDA, for guidance in developing review criteria for these HPV-based *in vitro* diagnostic devices.

Dr. Wilson then asked if there were any one else from the public that wanted to comment on the issues. There being no response, he closed the Open Public Hearing session.

National Institutes of Health Presentation

Penelope Hitchcock, DVM, of the National Institute of Allergy and Infectious Diseases, presented information on the role of HPV in cervical cancer. She discussed the incidence of HPV infection in men. She stated that control of cervical cancer was linked to regular Pap smear screening, and she noted the disparity in incidence rates for different ethnic populations. She discussed HPV testing/screening with respect to patient management in the United States from the standpoint of public health and expressed concern about HPV infection being designated as a reportable disease. She concluded that cervical cancer is a preventable disease and the highest priority is to eliminate this as a cause of cancer deaths for women. She stated that prevention and control of HPV infection will be achieved by vaccines, and microbicides.

FDA Presentations

Thomas E. Simms, a biologist in the Microbiology Branch, noted the FDA HPV review team and the CDC scientists that provided consults. He stated that the FDA had been approached by several manufacturers asking for advice on the appropriate studies to support approval for new indications for use of high-risk HPV subtype assays. The assays would be indicated as an initial general population screen for women 30 years and older and also in conjunction with Pap smear to detect the likelihood of cervical cancer. There was also interest in the use of alternative specimen sources such as self-collected vaginal swabs and urine. Mr. Simms provided information on cervical cancer incidence and mortality from the National Cancer Institute and the American Cancer Society and HPV prevalence in cervical cancer. He then reviewed indications and algorithms for interpretation of results for currently approved HPV testing devices. Mr. Simms presented statistics on high-risk HPV DNA test performance versus consensus histology results in CIN 2/3 women grouped by age and briefly reviewed issues raised from a review of the literature. He noted that Pap test result terminology does not appear to be applied consistently throughout the literature and there were other subjective diagnostic variations. For example, how the assay cutoff should be established and what the effect of HPV subtypes may be on an assay's performance characteristics.

Mr. Simms presented recommendations of the U.S. Preventive Services Task Force, the American Cancer Society, and the National Cancer Institute, none of which advocate routine screening for HPV for primary cervical disease screening. He added that a Centers for Disease Control Sexually Transmitted Diseases working group has

outlined three management options using HPV testing: triage of those with ASCUS Pap smear results, use as an adjunct to the Pap, and management of women with confirmed CIN. CDC has concluded that only triage of women with ASCUS Pap smear results could be supported by data. Mr. Simms also discussed a report of the British National Health Service Health Technology Assessment on HPV testing that was prepared from reviews of published literature. This report concluded that high-risk HPV testing is more sensitive than cytology for high-grade CIN, but has lower specificity than Pap testing and may only be appropriate in certain limited situations. This report recommended that larger ongoing studies should follow women for a minimum of five years and that a large randomized clinical trial was needed to evaluate the effect of HPV testing on cancer incidence and the length of protection afforded by a negative HPV test in conjunction with a negative cytology.

Kristen L. Meier, Ph.D., a mathematical statistician from the Division of Biostatistics, reviewed the claims under consideration. She explained the terminology and definitions of performance measures used in numerous published studies. She pointed out the confusion that existed because the terms used in statistics may have different meanings. For example, the measure of sensitivity may be defined as the ability of the test to detect HPV DNA (analytical sensitivity) or the ability to detect cervical cancer, or the ability to determine risk. Dr. Meier noted that studies should represent the intended (target) population and yield precise estimates of performance to minimize bias. She listed relevant factors that produce variation in test performance such as specimen type or collection device, noting that some factors are controllable and others inherent in practical use. She stated that using published studies to support HPV testing produces

problematic issues such as poolability and transferability. Dr. Meier concluded by suggesting some good study design principles to support claims such as clearly defined meaningful target conditions, clearly defined performance measures, and use of multicenter prospective well-designed study.

Marina Kondratovich, Ph.D., a mathematical statistician in the Division of Biostatistics, explained the statistical issues involved in the combination Pap test and HPV assay. She stated that if we determined that the reasonable measures of effectiveness of the test is sensitivity and specificity, then the target conditions of the disease should be defined. She noted that a combination of the Pap test with any test leads to an increase in sensitivity, and a decrease in specificity and combined tests are effective only if specificity does not decrease appreciably. She analyzed results of the earlier cited South African study in terms of Pap and HPV testing sensitivity and specificity results. She noted deficiencies of the models of Pap testing alone and simple combination of Pap plus HPV testing. She stated that because the HPV test was already approved for use in women with ASCUS and above, the real question is how to evaluate the effectiveness of HPV testing in women with normal Pap tests. She stated that this question could be answered by a randomized prospective clinical trial for women with normal Pap results. That trial should evaluate the effect of HPV testing on cancer incidence and the length of protection afforded by a negative HPV test in conjunction with the results of a normal Pap test.

FDA Presentation of Questions and Open Committee Discussion

Mr. Simms presented the FDA questions to the panel.

- 1) Are these appropriate indications for use? (For the use of HPV testing in conjunction with (age >30) or without (all age groups) Pap smear to determine the likelihood of high grade cervical disease and cancer)*

The panel suggested that the available published data did not demonstrate an appropriate sensitivity to use the assay for general screening. They recommended that the strength of HPV testing might be in the negative predictive value when interpreting results in conjunction with the Pap test.

- 2) What studies would be appropriate to support these intended uses?*

The panel agreed that studies should include patients with CIN II/III, patients with representative demographics of the U.S., should be multi-center, and should include a minimum of three thousand patients. The data should be accurate and should be designed to minimize bias.

- 3) What study endpoints are appropriate for use?*

The Panel suggested that results of Pap test readings, colposcopy, and biopsy be used as appropriate study endpoints. The Panel also expressed caution regarding the efficacy of HPV testing for the detection of adenocarcinoma since very little data exists regarding the sensitivity and specificity of the test to detect adenocarcinoma in situ or invasive adenocarcinoma.

- 4) Given that U.S. women represent a population that is highly screened by Pap test, what if any qualifications should be considered in the use of foreign data?*

The panel agreed that foreign data might be problematic if screening practices differed from those in the U.S. Studies should be done in a U.S. population, because the performance of the HPV test in an unscreened foreign population was not likely to be

equivalent to performance in a highly screened U.S. population. A foreign study may be used only as a model of the study population, to establish the feasibility of the testing algorithm.

- 5) *Should assay cut-off selection be adjusted to maximize sensitivity for disease rather than virus? If so, what compromises in specificity might be appropriate?*

The panel stated that because there were no actual data to evaluate, they could not provide answers to this question. Rule-out tests should emphasize sensitivity without compromising specificity, as much as possible. The statistician recommended that the data be analyzed using ROC curves.

- 6) *How can published studies be best used to support applications? How closely should populations in studies be matched to the proposed intended use population? What analysis of primary or raw data is appropriate?*

Current studies could be used to guide future studies and provide assumptions. It may not be appropriate to infer results from one study to another. Having raw data available is always important for analysis of published studies, and study evaluation may use a hierarchical Bayesian approach.

- 7) *What labeling would be appropriate for samples with normal Pap test results but HPV high- risk type reactive?*

This question was not addressed by the panel.

- 8) *If the HPV test does not specifically type, should the assay be labeled as presumptive or as a screening test? What other cautions or labeling caveats would be appropriate?*

The panel did not see the need to label tests as presumptive because the tests only apply to high-risk types.

9) *What studies would be appropriate for point of care or home self-collection?*

This question was deferred. The Panel suggested that the issue was important enough to warrant its own discussion.

Dr. Gutman asked the panel to consider whether existing published data was acceptable, in light of the regulatory requirement for approval pathways to be least burdensome.

Panel members answered that studies based on prospective longitudinal trials presented credible foundations. Raw data should be presented showing that the populations present comparable data and that the study criteria and methods meet those discussed during the panel session. Raw data from other studies on quality of life are also acceptable, but panel members warned that all published data must be presented, whether favorable to the test or not.

Open Public Hearing

Mark Schiffman of the National Cancer Institute stated that he was disturbed at the implication that there were no U.S. studies. He stated that there was a ten-year study underway of 24,000 women in Portland, Oregon. The endpoints are either histologically confirmed or cytologically verified CIN II/III. The data showed that there was complete protection for the first 2 ½ years following a double negative Pap test/HPV assay.

However, when questioned, he admitted that they had not biopsied the double negative women, so there was no histological confirmation for these cases.

After hearing final comments from the Panel, Dr. Wilson thanked the panel, the speakers, and the FDA, for their participation, and adjourned the session for the day at 4:00 pm.

I certify that I attended the Meeting of the Microbiology Devices Panel on December 8 2000, and that this summary accurately reflects what transpired.

Freddie Poole
Panel Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

Michael L. Wilson, M.D.
Panel Chair

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