

1 population, and the cancer rates in both places are  
2 radically different.

3 So I think that if anything there's a  
4 strength to a variety of studies and even though the  
5 data is not poolable, I think it reflects the nature  
6 of cervical cancer screening in the United States  
7 fairly well.

8 CHAIRMAN WILSON: Dr. Noller.

9 DR. NOLLER: I have a question and then a  
10 comment based on the answer to the question. Is the  
11 algorithm now part of the amendment?

12 DR. RELLER: Presumably the suggestion for  
13 the label change is part of what's being reviewed. So  
14 my suggestion and partial answer to this would be  
15 that --

16 (Pause in proceedings.)

17 DR. BERRY: That's an interesting answer.

18 (Laughter.)

19 MR. RELLER: -- would be that the  
20 algorithm should be part of the labeling.

21 CHAIRMAN WILSON: Okay. Any other  
22 suggestions or recommendations for the members of the  
23 panel?

24 DR. FELIX: I concur. I think that if  
25 found acceptable, clearly the issues that have been

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1 most important in our discussions have been the  
2 consequence of the positivity in the PAP negative  
3 patient. There has to be guidance for the user on  
4 that occurrence in the labeling.

5 CHAIRMAN WILSON: Any other comments?

6 DR. NOLTE: Well, the point that comes up  
7 when we talk about this a lot is that the labeling  
8 we're talking about goes into the package insert,  
9 correct? And the package insert is something that the  
10 laboratory sees as it does the test.

11 And the question is that's a fairly  
12 ineffective way to communicate that information to the  
13 physician that's actually receiving the information  
14 and having to interpret the test.

15 So it's one of those things, and it brings  
16 up to me the responsibility of the medical community  
17 versus the sponsor for establishing new -- pushing a  
18 certain set of practice guidelines in which there's an  
19 area that doesn't seem to be any real consensus.

20 When I heard the representative from ACOG  
21 stand up here and say there was no clinical value to  
22 HPV testing, I thought that was a bit of a -- that was  
23 a surprise to me because I always thought there was  
24 some clinical value to it.

25 But you know, what we're talking about

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1 here is how much clinical value and what sort of  
2 situations. And I just don't -- I guess I'm reluctant  
3 to put a big burden on the sponsor to do all of this  
4 by themselves knowing, number one, that it's going to  
5 be ineffectual, and number two, I'm not sure it's  
6 their responsibility.

7 CHAIRMAN WILSON: Okay. Any other  
8 comments or questions?

9 Dr. Reller.

10 DR. RELLER: Molecular assays, including  
11 hybrid capture PCR, have been of tremendous importance  
12 in understanding the potential viral role,  
13 pathogenesis of cervical carcinoma, and there is in --  
14 the hybrid capture test for HPV is approved.

15 So what I hear us discussing is what  
16 should be the criteria for extension of an indication,  
17 I mean, a further labeling deployment of a test that  
18 is already available.

19 But the central issue, it seems to me, is  
20 what data are there to alter clinical practice based  
21 on the test so that the availability of this test  
22 would enable the studies for refinement of extant  
23 guidelines.. Btu we don't have those data available  
24 that would enable an appropriate guidance to be put  
25 into the labeling, and until those data are available,

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1 it seems to me, we have a test that's been approved by  
2 the FDA. It's available for doing the longitudinal  
3 studies that would be required; that the tools or at  
4 least one tool -- it's not the only tool, PCR, other  
5 things -- the tools are available to refine the  
6 guidelines, but until one has the studies that would  
7 enable that refinement, these are tools, and we should  
8 not be putting into labeling what would, in essence,  
9 be alter guidelines based on no data that proves their  
10 applicability.

11 CHAIRMAN WILSON: Thank you, sir.

12 All right. At this point we'd like to go  
13 ahead and take our regularly scheduled break. One,  
14 they'd like to still do some more work on the sound  
15 system, but also we'd like to give both the sponsor  
16 and FDA time to polish up their responses and make  
17 sure everything is working.

18 So let's reconvene as close as we can to  
19 about ten minutes after the hour.

20 Thank you.

21 (Whereupon, the foregoing matter went off  
22 the record at 2:51 p.m. and went back on  
23 the record at 3:11 p.m.)

24 CHAIRMAN WILSON: Okay. At this point I'd  
25 like to open the second public hearing. Any member of

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1 the public who would like to make a comment may do so  
2 at this time.

3 (No response.)

4 CHAIRMAN WILSON: Okay. There being none,  
5 we'll close the open public hearing.

6 We'll move into the industry response. At  
7 this time the sponsor may provide comments to respond  
8 to any issue that's been raised during the committee  
9 discussions.

10 And I would note that this is limited to  
11 five minutes.

12 DR. KINNEY: I want to take one minute of  
13 that five for a couple of purposes. The first one is  
14 to talk about the issue that you raised about the  
15 relationship of ACOG to new technology and the  
16 Practice Committee. As a Fellow of the college, I  
17 think that I'm permitted to talk about that.

18 They don't have access to the data that  
19 this panel does. They're only permitted to consider  
20 peer reviewed published articles, and then there's a  
21 substantial deliberative period after the article has  
22 been published.

23 To give you an idea about what the time  
24 line is like, in 1997 we had clear evidence that  
25 hybrid capture II was useful for triage. In 1999, a

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1 similar panel reviewed that information and agreed.  
2 In 2002, ACOG is still deliberating over whether or  
3 not that's, in fact, the case. And they'll come  
4 along. They're just not there yet, partly because  
5 they don't have access to the same information.

6 The other issue has to do with there's  
7 been a lot of discussion about false positives and the  
8 concern about the adverse effects associated with  
9 having to do 15 tests on the average to pick up one  
10 woman with disease, and that's a meaningful issue only  
11 if the consequences of being found to have HPV are  
12 really adverse.

13 If in fact this is used in the fashion  
14 that we have suggested, the adverse consequences are  
15 limited to having an annual PAP smear, which I think  
16 the members of the Panel that practice cytopathology  
17 would tell you is a perfectly acceptable notion.

18 That leave out the issues of provider  
19 education, which we talked about is important and is  
20 the single hardest thing that we do, but I don't think  
21 that that's a reason not to give us this tool

22 DR. COX: I have several points.

23 A prospective clinical study to answer the  
24 questions that would be ideal according to many  
25 members of the committee, in particular, with an

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1 endpoint of cervical cancer detection is obviously  
2 just not feasible. I don't think that's something  
3 that can be done in this country.

4 I think that is a concern always to submit  
5 women to excessive colposcopy. I've always felt that  
6 way, but I do believe that this can be handled through  
7 education, and that I'm more concerned about the three  
8 to 4,000 women who lose their lives every year due to  
9 cervical cancer or at least get cervical cancer --  
10 I'll put it that way -- that have had reasonable  
11 screening.

12 I believe that we can make a significant  
13 impact on that and that we should not deny them that  
14 potential. And there was also a suggestion that  
15 clinicians could just go ahead and use this test this  
16 way without having an indication approved because it's  
17 already approved in ASCUS management.

18 But I believe that approval in this  
19 particular adjunctive situation with PAP and primary  
20 screening has very important public health  
21 implications that exceeds greatly the importance of  
22 previous approval in ASCUS management, and approval  
23 here would be a confirmation of this.

24 And finally, as with any new indication,  
25 there has to be guidelines developed and will be

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1 developed. They are usually not developed before an  
2 indication is given, and as one who serves on several  
3 guidelines committees, I believe quickly these  
4 committees will respond to develop via the best  
5 literature available throughout the world guidelines  
6 on the use of HPV testing in conjunction with the PAP.

7 And I believe that labeling cannot be any  
8 stronger in its recommendation than what we have put  
9 forth here because until those guidelines have been  
10 developed both by professional organizations, this  
11 will be up to clinician discretion and guided by the  
12 education that we can provide in respect to guideline  
13 group input.

14 DR. LORINCZ: I'll make some concluding  
15 remarks.

16 Speaking on the company, they are  
17 scientists with extensive experience in the field of  
18 HPV diagnostics. So we maintain that our data from  
19 these eight diverse studies support the proposed claim  
20 for adjunctive use of HPV testing with the PAP test in  
21 women over the age of 30 in the U.S.

22 The FDA present that their concerns  
23 related to a variety of biases, the most important of  
24 which appear to be device bias and verification bias.

25 With respect to the first of these biases,

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1 the use of alternative collection devices, we have  
2 presented data that indicate the CVL bias against the  
3 added HPV test. Yet we were still able to show a  
4 large improvement in sensitivity in the Portland  
5 study.

6 It's our opinion that the analyses show  
7 that the FDA concerns, while mitigating to some extent  
8 the apparent value of our presentations, do not  
9 introduce a sufficient level of concern to change the  
10 take home message.

11 It is precisely the diversity of the study  
12 sites, collection devices, ethnic groups, et cetera,  
13 that demonstrate the robustness of the Digene hybrid  
14 capture HPV test as an adjunct to the PAP. To state  
15 it succinctly, we observe the same trends of  
16 improvement when adding HPV testing to the PAP in all  
17 of these studies.

18 With respect to the second perceived  
19 important bias, verification bias, we do not believe  
20 that adjustments for this bias change the fact that  
21 HPV plus PAP is a much more sensitive test than the  
22 PAP alone.

23 It is the opinion of our statisticians  
24 that the use of overly conservative verification bias  
25 adjustment is not a reasonable approach as it uses

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1 only part of the information available and applies the  
2 worst case assumptions to all of the data.

3 Even with the worst case assumptions,  
4 three of our studies met the previously agreed  
5 criteria of improvement.

6 The Digene HPV test will provide several  
7 clinical benefits. Perhaps the most important, it  
8 will allow an objective classification of women into  
9 low risk versus high risk groups. There is no  
10 recommended change in screening intervals beyond those  
11 currently in place in the U.S.

12 We confirm that the proposed algorithm as  
13 presented today will be part of the labeling if  
14 allowed by the FDA and will allow us to embark upon  
15 extensive education measures.

16 I'd like to conclude by reminding you all  
17 that there was a remarkable level of concordance among  
18 the eight studies in terms of key parameters and the  
19 final overall conclusions, namely, that HPV added to  
20 the PAP test produced a large gain in sensitivity that  
21 was much greater than expected by chance alone.

22 Furthermore, this gain in sensitivity was  
23 accompanied by only a minor decrease in specificity  
24 which Digene maintains is a worthwhile tradeoff for  
25 the clinicians and the women of this nation.

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1 Thank you.

2 CHAIRMAN WILSON: Thank you very much.

3 At this time we'd like to have the FDA's  
4 comments.

5 DR. GUTMAN: Well, I'd like to thank the  
6 sponsor for providing us with an interesting and  
7 challenging set of data and for their cogent  
8 presentation this morning.

9 And I'd like to thank my colleagues at the  
10 FDA for putting on the table what we view is the  
11 appropriate questions and issues. The agency  
12 obviously does think HPV testing is pretty important.  
13 We've approved this test already for use in a subset  
14 of normal PAPs, and we brought you up here from all  
15 across the country to get your best advice fair and  
16 square on an extension of the claim to use this in the  
17 subset or the large subset of women who have negative  
18 PAP smears.

19 It is important to the agency that we  
20 insure rapid technology transfer. It is important to  
21 the agency that new intended uses be rapidly  
22 available, and of course, it's important to the agency  
23 also that these be grounded in safety and  
24 effectiveness, and Ms. Poole will be actually reading  
25 you the definitions of safe and effectiveness shortly

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1 as you approach the final vote.

2 For IVDs, I think it's self-evident that  
3 there's a unique link between safety and effectiveness  
4 in that the safety and effectiveness are always around  
5 the recurrent theme of true versus false positives and  
6 true versus false negatives, and what the information  
7 content has in terms of information impact on the  
8 patient.

9 This has been a challenging submission for  
10 us. It's been, I'm sure, challenging for the sponsor,  
11 and it will be challenging and has been challenging  
12 for you because of what is known and not known about  
13 the performance of the device itself and what is known  
14 and not known about the implications of the use of  
15 this device in this new setting,

16 We appreciate the wisdom, the advice  
17 you've already given before to the wisdom of your vote  
18 in determining whether the data set establishes safety  
19 and effectiveness and makes this test ready for prime  
20 time or whether, indeed, more or different data is  
21 needed.

22 Thank you.

23 CHAIRMAN WILSON: Thank you, Dr. Gutman.

24 Okay. At this time we'd like to move to  
25 the final recommendation, and Ms. Poole will give us

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1 both the guidelines on the voting as well as a list of  
2 the voting members on the panel today.

3 MS. POOLE: The regular voting members  
4 seated at the table this afternoon are Dr. Kathleen  
5 Beavis and Dr. Laura Koutsky.

6 Appointment to temporary voting status, I  
7 have a memorandum to read from Dr. Feigel.

8 "Pursuant to the authority granted under  
9 the Medical Devices Advisory Committee, charter dated  
10 October 27, 1990, and as amended August 18th, 1999, I  
11 appoint the following persons as voting members for  
12 the Microbiology Devices Panel for the duration of  
13 this Panel meeting on March 8th, 2002: Donald Berry,  
14 Juan Felix, Frederick Nolte, Barth Reller, George  
15 Birdsong, and Janine Janosky.

16 "For the record, these people are special  
17 government employees and are either a consultant to  
18 the Panel or are a consultant or voting member of  
19 another panel under the Medical Devices Advisory  
20 Committee. They have undergone the customary conflict  
21 of interest review. They have reviewed the material  
22 to be considered at this meeting."

23 And it signed David W. Feigel, Jr., March  
24 5th, 2002, Director, Center for Devices and  
25 Radiological Health.

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1           The recommendations for voting on a  
2 premarket approval application or supplement. The  
3 medical devices amendments to the Federal Food, Drug,  
4 and Cosmetics Act, "the Act," as amended by the Safe  
5 Medical Devices Act of 1990, allows the Food and Drug  
6 Administration to obtain a recommendation from an  
7 expert advisory panel on designated medical device  
8 premarket approval applications that are filed with  
9 the agency. The PMA must stand on its own merits, and  
10 your recommendations must be supported by safety and  
11 effectiveness data in the application or by applicable  
12 publicly available information.

13           Safety is defined in the act as a  
14 reasonable assurance, based on valid scientific  
15 evidence, that the probable benefits to health under  
16 conditions of intended use outweigh any possible risk.

17           Effectiveness is defined as a reasonable  
18 assurance that in a significant portion of the  
19 population the use of the device for its intended uses  
20 and conditions of use when labeled will provide  
21 clinically significant results.

22           Your recommendation options for the vote  
23 are as follows:

24           Approval if there are no attached  
25 conditions;

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1                   Approvable with conditions. The Panel may  
2 recommend that the PMA be found approvable subject to  
3 specified conditions, such as physician or patient  
4 education, labeling changes, or a further analysis of  
5 existing data.

6                   Prior to voting all of the conditions  
7 should be discussed by the Panel.

8                   Not approvable. The Panel may recommend  
9 that the PMA is not approvable if the data do not  
10 provide a reasonable assurance that the device is safe  
11 or if a reasonable assurance has not been given that  
12 the device is effective under the conditions of use  
13 prescribed, recommended, or suggested in the proposed  
14 labeling.

15                   Following the voting, the Chair will ask  
16 each Panel member to present a brief statement  
17 outlining the reasons for their vote.

18                   CHAIRMAN WILSON: Okay. At this time, I'd  
19 like to read the proposed indication for us as  
20 provided by the FDA. It states that as a general  
21 population screening test, in conjunction with the PAP  
22 smear, for women ages 30 years and older as an aid to  
23 determine the absence of high grade cervical disease  
24 or cancer.

25                   It further states that in women in a

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1 concurrent normal PAP smear and a negative HC2 HPV  
2 result, the probability of detecting evidence of high  
3 grade cervical disease upon colposcopy is reduced  
4 relative to normal PAP smear results alone based on  
5 the increased negative predictive value of the  
6 combined use of both methods. This result is not  
7 intended to deter the patient from proceeding to  
8 colposcopy should other clinical indicators warrant  
9 such action.

10 Okay. Given Ms. Poole has stated there  
11 are three potential ways that the committee can vote,  
12 at this time I'd like to open it for motions.

13 Dr. Reller.

14 DR. RELLER: I move that we find the  
15 requested supplement not approvable.

16 CHAIRMAN WILSON: We have a motion for a  
17 vote for not approvable. Is there a second to that  
18 motion?

19 DR. BEAVIS: I'll second that.

20 CHAIRMAN WILSON: We have a motion and a  
21 second. Is there any further discussion or comments  
22 by the members of the Panel?

23 Dr. Berry.

24 DR. BERRY: Yes, I have a question. If I  
25 wanted to vote approvable with conditions, how should

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1 I vote on this motion?

2 CHAIRMAN WILSON: You would vote nay on  
3 this motion.

4 Are there any further questions or  
5 comments?

6 (No response.)

7 CHAIRMAN WILSON: Okay. I'd like to call  
8 the vote then.

9 Dr. Reller has moved and it's been  
10 seconded that we vote not approvable. All those in  
11 favor signify by raising their hands please.

12 We'll do it by voice. Dr. Reller?

13 DR. RELER: Just a clarification. You  
14 mentioned in our instructions that not only must we  
15 vote, but also that we must give the rationale for our  
16 vote.

17 CHAIRMAN WILSON: Yes, following the vote,  
18 correct.

19 DR. RELER: So after the vote is when we  
20 give the rationale?

21 CHAIRMAN WILSON: Yes, yes. We just need  
22 to go through one by one on our vote.

23 DR. FELIX: Can I ask -- can I ask you to  
24 repeat the indication?

25 CHAIRMAN WILSON: The intent of the

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1 proposed indication?

2 DR. FELIX: Yes.

3 CHAIRMAN WILSON: Okay. I'd be happy to.

4 The proposed indication for use is that as  
5 a general population screening test in conjunction  
6 with a PAP smear for women ages 30 years and older as  
7 an aid to determine the absence of high grade cervical  
8 disease or cancer. In women with a concurrent normal  
9 PAP smear and a negative HC2 HPV result, the  
10 probability of detecting evidence of high grade  
11 cervical disease upon colposcopy is reduced relative  
12 to a normal PAP result alone based on the increased  
13 negative predictive value of the combined use of both  
14 methods.

15 This result is not intended to deter the  
16 patient from proceeding to colposcopy if the clinical  
17 indicators warrant such action.

18 Are there any other questions or any other  
19 points that the Panel members would like to have  
20 clarified?

21 (No response.)

22 CHAIRMAN WILSON: Okay. So we'll proceed  
23 around to the voting members then first. Dr. Reller.

24 DR. RELLER: I vote in favor of the  
25 motion.

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1 CHAIRMAN WILSON: Dr. Berry.  
2 DR. BERRY: No.  
3 CHAIRMAN WILSON: Dr. Janosky.  
4 DR. JANOSKY: Yes.  
5 CHAIRMAN WILSON: Dr. Felix.  
6 DR. FELIX: No.  
7 CHAIRMAN WILSON: Dr. Koutsky.  
8 DR. KOUTSKY: No.  
9 CHAIRMAN WILSON: Dr. Beavis.  
10 DR. BEAVIS: Yes.  
11 CHAIRMAN WILSON: Dr. Nolte.  
12 DR. NOLTE: No.  
13 CHAIRMAN WILSON: And Dr. Birdsong?  
14 DR. BIRDSONG: Could I ask for a  
15 clarification on that before I --  
16 CHAIRMAN WILSON: Go ahead.  
17 DR. BIRDSONG: We are voting on Dr. --  
18 CHAIRMAN WILSON: Reller's motion that  
19 this test be classified as not approvable.  
20 DR. BIRDSONG: I vote no.  
21 CHAIRMAN WILSON: Vote no.  
22 Okay. The motion does not carry, the vote  
23 being three votes for and five votes against.  
24 Let's still go ahead and go around and  
25 have each person give their reason for their voting on

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1 this motion.

2 Dr. Reller.

3 DR. RELLER: The FDA has previously  
4 considered this to be an approvable test for the  
5 indication of detection of HPV, and that I think is,  
6 you know, accepted, and it gives us a tool to have the  
7 studies conducted that would enable us to have an  
8 accurate database for this supplement.

9 The data that we heard presented do not  
10 provide that database, and until we have how this test  
11 is to be deployed, that is, what is the practitioner  
12 to do differently based on this test. Negative, X  
13 period of interval between giving repeat PAP smear;  
14 positive, X period. Until the data supporting those  
15 specific recommendations for alteration of practice  
16 are in hand, I think we have nothing more than what we  
17 have now, namely, a test that is of demonstrated value  
18 for proving the presence of an agent that is highly  
19 associated with or, even put another way, without  
20 which there is evidence with the high risk viral types  
21 that one doesn't get cervical carcinoma, which is a  
22 necessary, though not sufficient, ingredient.

23 So the bottom line is that it's a good  
24 test, but we do not have the data for alteration in  
25 the deployment of the test in clinical practice, which

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1 to me is the essence of the request for the amendment.

2 CHAIRMAN WILSON: Okay. Dr. Berry.

3 DR. BERRY: Dr. Reller voted not to  
4 approve. I voted against that. My arguments are  
5 almost identical to his.

6 I agree completely with what he said, and  
7 I think it's being a bit picky about what is  
8 approvable with conditions, and so my conditions are  
9 really quite strong and I'll tell you about what they  
10 are the next time around, although I'm a little bit  
11 worried that I'm going to vote against everything,  
12 including motions to approve.

13 Just one correction of something that I  
14 said. I said an average of 15 false positives per  
15 true positive. It's really 25 to one. I misspoke.

16 Dr. Cox said about the one that women lose  
17 their lives, and see, I don't think anything like that  
18 has been shown. This one true positive, what is the  
19 medical management of that patient? Would she have,  
20 for example, had a PAP smear the following year and  
21 found that she had precursors to cancer and treated  
22 accordingly? Losing their lives has not been shown in  
23 the submission.

24 Just to say again what Dr. Reller or my  
25 version of what Dr. Reller said, it is not clear from

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1 the submission how the test should be used, and it is  
2 not clear from the submission how the test will be  
3 used, and those will provide the basis for my  
4 conditions next time around.

5 CHAIRMAN WILSON: Thank you.

6 Dr. Janosky.

7 DR. JANOSKY: I actually had a similar  
8 assessment. I see a test, and I see a test that's  
9 detecting, but I'm not so sure what that tells me in  
10 terms of what should happen in clinical care, what  
11 should be the outcome from the test.

12 In terms of having it list for the  
13 indications, that's why I voted to note approve.

14 CHAIRMAN WILSON: Thank you.

15 Dr. Felix.

16 DR. FELIX: I voted against the motion  
17 because, one, the indication that they're requesting,  
18 that the sponsors are requesting is limited and  
19 doesn't go into many of those things that are most  
20 suggested by Dr. Reller. It's actually very limited  
21 in its scope.

22 And just reading it, everything that they  
23 say in their indication has actually been proven.  
24 That's why I voted.

25 CHAIRMAN WILSON: Thank you.

1 Dr. Koutsky.

2 DR. KOUTSKY: I voted no because I feel  
3 that the information we were given documented the  
4 indication that there was evidence supporting the  
5 indication for use.

6 I also thought long and hard about the  
7 issue of a perfect trial, and having just participated  
8 in ALTS, which I think was about as perfect as you can  
9 get, it essentially replicated what Walter Kinney had  
10 shown in a Kaiser study and several other smaller  
11 studies have shown, and with thinking about randomized  
12 clinical trial, the concern always comes down to I do  
13 -- because of the studies I'm doing, we're trying to  
14 take into account verification, but there isn't a good  
15 way to do it. You are left with data that will always  
16 be imperfect, and the question becomes how much more  
17 imperfect data do we need.

18 CHAIRMAN WILSON: Thank you.

19 Dr. Beavis.

20 DR. BEAVIS: I voted in favor of the  
21 motion to reject for a few reasons. One, I don't feel  
22 that the data are present in the current submission,  
23 and I'm brought back to the two things that we're  
24 supposed to be considering, and that's the safety and  
25 the efficacy part of our charge.

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1                   And in going directly to the efficacy, and  
2                   again, this is just my notes from what was said, we're  
3                   supposed to have a significant portion of the  
4                   population and that this will provide clinically  
5                   significant results.

6                   And I don't think it's been demonstrated  
7                   how these results are going to be used clinically, and  
8                   therefore whether these results are clinically  
9                   significant.

10                   CHAIRMAN WILSON: Thank you.

11                   And Dr. Nolte.

12                   DR. NOLTE: And I voted against the  
13                   motion. Primarily it's based on a couple of things.  
14                   I recognize from looking through the 47 pounds of data  
15                   that HPV presence and absence of cytological findings;  
16                   imparts a significantly higher risk of cervical  
17                   cancer.

18                   Also, I really wish we would have had a  
19                   well controlled, well designed study to prove the  
20                   point, the extension of the application of this test,  
21                   but that wasn't the case.

22                   But even with that, in all the problems  
23                   pointed out by both the sponsor and the FDA, the  
24                   message still comes through that there is a  
25                   significant contribution in terms of sensitivity with

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1 no real adverse effect on specificity of the HPV test  
2 when done in conjunction with PAP.

3 CHAIRMAN WILSON: And Dr. Birdsong.

4 DR. BIRDSONG: I voted against the motion  
5 because if I understand the concerns expressed, and  
6 I've previously expressed some of my own, I think the  
7 overriding concern for me, you know, is cancer  
8 detection, and the studies done in a variety of  
9 settings were ending up all imperfect, but in a  
10 variety of settings have shown improvement in the  
11 negative predictive value and improvement or a  
12 demonstration I think we should say that the relative  
13 risk of the patients who have high risk HPV is -- the  
14 relative risk is higher for the patients who are high  
15 risk infected with high risk types, and so this will  
16 improve cancer detection.

17 I think, you know, there are a lot of  
18 issues that will arise out of doing this, and while I  
19 think the clinicians who spoke on behalf of the  
20 sponsor are ready for them and, you know,  
21 understanding what the issues are, I think there are  
22 a lot of clinicians out there who are not. But that  
23 wouldn't justify voting to not approve the proposal.

24 CHAIRMAN WILSON: Thank you for your  
25 comments.

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1                   And at this point, the motion having been  
2                   defeated, we will entertain further motions.

3                   DR. BERRY: I would like to move that it's  
4                   approvable with conditions.

5                   DR. FELIX: Second.

6                   DR. BERRY: Well, you haven't heard my  
7                   conditions yet.

8                   (Laughter.)

9                   MR. BERRY: Maybe, Juan, you have  
10                  conditions. Would you like to do conditions?

11                  CHAIRMAN WILSON: We need to hear the  
12                  conditions first.

13                  DR. BERRY: I have two conditions. First  
14                  of all, I am persuaded in the efficacy of the test,  
15                  and I think Dr. Lorincz's statement that the  
16                  concordance of the various studies is absolutely  
17                  correct. I think this is a truly fine test.

18                  The issue to me is the one that Dr. Reller  
19                  stated, and I don't know whether the condition that  
20                  I'm going to specify can be met. I would like to see  
21                  specific recommendations for using the test  
22                  clinically, and I would like to see a demonstration  
23                  that these recommendations will have an impact on  
24                  clinical practice.

25                  CHAIRMAN WILSON: Dr. Berry, could you

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1 just repeat those for us so people can get this down?

2 Thank you.

3 DR. BERRY: I would like to see specific  
4 recommendations for using the test in clinical  
5 management, and I would like to see a demonstration  
6 that they will have an impact on clinical practice.

7 CHAIRMAN WILSON: Dr. Gutman?

8 DR. GUTMAN: Yeah. I actually need some  
9 clarification on this. Is this something that you are  
10 looking for before or after approval? And is this  
11 something that you're looking for in terms of some  
12 kind of expert assessment, a clinical study, a  
13 maculating adventure or some other alternative?

14 DR. BERRY: Well, I was not looking for  
15 expert opinion. I was looking for an evidence based  
16 demonstration that could be, in part, or perhaps in  
17 whole, based on the information that they currently  
18 have. For example, the longitudinal data analysis  
19 that we talked about this morning and the  
20 recommendation consistent with the conclusions of that  
21 longitudinal data analysis.

22 What I'm worried about is that this gets  
23 out into the world and nobody knows anything about how  
24 to do things. Yes, you say you're going to education,  
25 but you know, being an educator from long past, I'm

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1 not too optimistic about the effects of telling people  
2 how they should do things.

3 I would like to see a specific indication,  
4 a specific recommendation that says if you, for  
5 example, if you prolong the interval -- and I'm not  
6 saying that this is part of the condition, but this is  
7 just an example -- if you prolong the interval for  
8 those patients who test -- for those women who test  
9 negative and you shorten the interval for those  
10 patients who test positive on HPV, that that will --  
11 and some modeling based on data -- that will improve  
12 the management of patients, and I'm not looking for a  
13 randomized trial that will show cervical cancer  
14 mortality reduction or anything like that, but some  
15 evidence based demonstration that the recommendations  
16 that the claim is justified

17 CHAIRMAN WILSON: Dr. Durack, did you have  
18 a question?

19 DR. DURACK: Mr. Chairman, is it  
20 permissible for a non-voting member to ask for a  
21 clarification on the wording of the conditions?

22 CHAIRMAN WILSON: Yes, it is.

23 DR. DURACK: Dr. Berry, I wonder if you  
24 would entertain instead of impact on clinical  
25 practice, positive impact on outcome of clinical

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1 interventions?

2 DR. BERRY: Absolutely. Thank you very  
3 much. I would accept that.

4 CHAIRMAN WILSON: Dr. Gutman? How  
5 would --

6 DR. GUTMAN: You've just taken words away  
7 from him. I'm not sure how to respond.

8 It's a daunting challenge to ask the -- I  
9 guess I'd be curious to hear if the company has ideas  
10 on how they might address this.

11 PARTICIPANT: Are you looking for  
12 something now?

13 (Laughter.)

14 DR. GUTMAN: Never mind.

15 CHAIRMAN WILSON: I think Dr. Gutman is  
16 just looking for clarity about how this would be  
17 achieved.

18 Dr. Janosky.

19 DR. BERRY: It could be a post market  
20 study. It could be data that they currently have. It  
21 could be, you know, a new study.

22 CHAIRMAN WILSON: Dr. Janosky?

23 DR. JANOSKY: I have a question for Dr.  
24 Gutman. It seems like what this motion is asking is  
25 for us to do approvable with conditions. Oh, by the

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1 way, the condition is come up with a clinical  
2 indication. Is that what it is?

3 DR. GUTMAN: Sort of, yeah.

4 DR. JANOSKY: So you're saying you have a  
5 product, but you don't have a clinical indication.  
6 Come up with one and then it's approvable.

7 I would think that this is not within the  
8 line of conditions that we typically attach to this  
9 type of motion. Am I incorrect?

10 DR. GUTMAN: This is at the edge.

11 DR. JANOSKY: That's what I thought.

12 (Laughter.)

13 DR. JANOSKY: So you're telling them to  
14 find another indication and then we'll prove it. I  
15 would submit that it's a little bit further than the  
16 edge.

17 CHAIRMAN WILSON: Dr. Reller, comment  
18 please?

19 Actually, no. You may not comment in the  
20 vote. sorry.

21 Dr. Reller.

22 DR. RELER: I am in full support of the  
23 conditions that Dr. Berry outlined, and Dr. Gutman  
24 delineated were at or beyond a condition as opposed to  
25 grounds for not approving with the data currently

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1 available.

2 In everything I've heard today, the PAP  
3 smear is what detected an abnormality that  
4 necessitated action. There may be action that is  
5 necessitated by a positive HPV HC2 test. That could  
6 be a repeat PAP smear at a certain interval. It could  
7 be colposcopy at a certain interval. It could be one  
8 of several things that would alter clinical practice  
9 based on a positive test.

10 But I have not heard nor seen the data to  
11 support the specific indications that are at the heart  
12 of what Dr. Berry would like to see before approvable.  
13 If we had those, we may well have an approvable test.  
14 It's just at ten minutes of four on the 8th of March  
15 2002 I don't think we have that, and I think if we're  
16 going to get it, it would be a condition of approval  
17 which would be before approval, which would de facto  
18 put us back to we do not have an approvable test  
19 without further information.

20 CHAIRMAN WILSON: Dr. Felix.

21 DR. FELIX: I'm sorry. I think I'll  
22 disagree with what you said because, in fact, I think  
23 four of the eight studies presented data of an  
24 intervention that was not caused by the PAP. In most  
25 of those studies a HPV positive resulted in a

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1 colposcopy to detect the disease or it did not detect  
2 disease, but it was, in fact, a trigger for  
3 colposcopy.

4 Now, the company has chosen not to use  
5 that as an indication or has not chosen to use that as  
6 their algorithm for treatment suggestion, but there is  
7 data there that intervention due to HC2 positivity  
8 does detect disease.

9 DR. RELER: Are you saying, Dr. Felix,  
10 that if you have an HPV positive test that a woman  
11 should have colposcopy?

12 DR. FELIX: No, I'm not saying that. I  
13 just said you mentioned that there was no disease  
14 found other than with the PAP smear, and I was just  
15 correcting you.

16 DR. RELER: Okay, but this is exactly the  
17 point. Does an HPV positive test -- should it trigger  
18 colposcopy? Should it trigger a repeat PAP smear?  
19 What is the action that the practitioner is to take  
20 based on the HPV test positive?

21 That to me is the critical issue, and yes,  
22 I recognize that colposcopy in these studies found  
23 something that the PAP did not. However, then the  
24 logical extension would be you have a positive; you do  
25 colposcopy. But if you're not willing to go there,

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1 then where do we go?

2 And I don't see the guidelines for what to  
3 do with the positive test.

4 CHAIRMAN WILSON: Dr. Koutsky.

5 DR. KOUTSKY: As neither a gynecologist or  
6 a pathologist, I find myself in the middle of these  
7 discussions all the time because it seems that you've  
8 got gynecologists not wanting the pathologists to give  
9 them recommendations for follow-up, and there's this  
10 whole debate about who should give the recommendations  
11 and what should be followed.

12 I don't see where this is any different  
13 than with an ASCUS or an out cell PAP (phonetic).  
14 Depending on your patient population, there are  
15 decisions made about whether you're going to bring her  
16 in every four months, whether you're going to bring  
17 her in every six months or you're going to refer  
18 immediately to colposcopy.

19 I also have to question this issue of we  
20 don't have a clinical indication. Either we decide  
21 CIN3 is something that's clinically important to  
22 detect or we throw out all cervical cancer screening,  
23 and you know, these data have suggested an increase  
24 sensitivity with a combined PAP and hybrid capture II  
25 testing for detecting CIN3.

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1           Issues around who should get immediate  
2 . colposcopy, who can wait for a year for a follow-up  
3 PAP, I think it seems reasonable at this point to  
4 leave that other discussion as to whether or not this  
5 indication is appropriate.

6           CHAIRMAN WILSON: Dr. Birdsong.

7           DR. BIRDSONG: This is a little bit of  
8 just a semantic comment, but there's been a question  
9 raised as to whether or not the company has provided  
10 sufficient or indicated what the appropriate  
11 indications were for the test is, and the indication,  
12 as I understand it from reading all of the material,  
13 is screening for cervical cancer along with the PAP  
14 smear in women age 30 and older. You know, that's an  
15 indication.

16           What they haven't provided and what is  
17 admittedly a little bit problematic is what to do with  
18 the results, and in light of that is they've given  
19 some guidance, but that's really more the -- that role  
20 is more appropriately taken by the professional  
21 organization, and the pathologists and gynecologists,  
22 you know, should continue that argument as to when to  
23 do what.

24           But you know, I don't think it's  
25 necessarily their role to lay out the entire algorithm

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1 as to how the test result is to be used, although it  
2 might be helpful if they did that. I don't think that  
3 should be a requirement of the company.

4 CHAIRMAN WILSON: Dr. Nolte.

5 DR. NOLTE: We were having this discussion  
6 earlier about the previous indication for the test and  
7 its use in screening women, looking at women with  
8 ASCUS, and although that's an indication, I mean, the  
9 extent to which that indication is put into medical  
10 practice is variable at best.

11 And I keep coming back to the fact that I  
12 don't think it's reasonable to expect the sponsor to  
13 map out the clinical practice plan. They've got clear  
14 indication now, and in practice that clear indication  
15 or that -- I'd be curious to see how many HPV tests  
16 are sold versus the number of cases of ASCUS that  
17 occur in this country, but I think you'd find that  
18 there are many practice settings that even that  
19 indication isn't adhered to with any regularity.

20 CHAIRMAN WILSON: Thank you.

21 Any other comments?

22 I'd just like to restate the motion at  
23 this time so everyone knows exactly what we're talking  
24 about.

25 There's a motion for approvable with

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1 conditions, there being two conditions. The first  
2 thing that there be provided specific recommendations  
3 for using the test clinically, the second being a  
4 demonstration that these recommendations will have a  
5 positive impact on clinical outcomes.

6 Dr. Koutsky.

7 DR. KOUTSKY: The positive impact on  
8 clinical outcomes, are we back into preapproval, post  
9 marketing?

10 CHAIRMAN WILSON: I think that's an issue  
11 in Dr. Gutman's square.

12 DR. GUTMAN: Well, it's your -- we're  
13 looking for a recommendation from you. That makes a  
14 difference to us and to the company.

15 DR. KOUTSKY: It was your condition. What  
16 did you want it to be?

17 DR. BERRY: Well, I'm open, but the intent  
18 was preapproval.

19 DR. DURACK: Mr. Chairman.

20 CHAIRMAN WILSON: Yes, Dr. Durack.

21 DR. DURACK: May I just make a general  
22 comment? As industry representative, I would like to  
23 give an opinion, which is that if we set conditions,  
24 we have to just be careful that they're not unduly  
25 burdensome or put the sponsor in a position where they

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1 would like to meet the conditions, but are unable to  
2 for some reason beyond their control, such as ACOG.

3 I just put that on the table, without  
4 agreeing or disagreeing with any of the points that  
5 we're voting.

6 CHAIRMAN WILSON: Good point. Thank you.

7 Dr. Gutman, what are the general  
8 mechanisms that would allow FDA to work with the  
9 sponsor to try to accommodate these recommendations?

10 DR. GUTMAN: Well, the reason I'm trying  
11 to reach clarity is that if you are really pushing for  
12 a study that would be at all broad in scope for  
13 evidence based demonstration of recommendations and,  
14 frankly, positive impact on outcomes. We would be  
15 putting a very challenging task both before the agency  
16 and before the company.

17 I'm thinking about our clock actually and  
18 the fact that maybe that would require a new  
19 prospective study or something.

20 If we're talking about piecing together  
21 language or arguing over language and trying to get  
22 the company to provide some evidence of some modeling  
23 or drawing back from the claim actually, not  
24 strengthening the algorithm, but that's weakening it  
25 and just putting what's there and what's not there.

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1 That's something we could probably negotiate in real  
2 time with the company. It might be awfully bloody,  
3 but we could probably do it.

4 And there are all kinds of choices in  
5 between, but my preference would be to do less rather  
6 than more if you make it a preapproval because time  
7 clicks for both us and the companies, which can make  
8 a high hurdle. That's going to be a problem for me  
9 personally. I'll do whatever you would advice or at  
10 least I'll consider whatever you advise.

11 And if you make it post market, I don't  
12 want to over sell the strength of that not only  
13 because of ACOG, but just because of challenges of the  
14 nuances of practice and the law and the regulations  
15 and the company's interest. It's challenging to  
16 gather information post market, but both are possible.

17 CHAIRMAN WILSON: But, Dr. Gutman, does it  
18 meet the spirit of the process at this point to  
19 require up front data on positive clinical outcomes?  
20 Because, in effect, it's almost a resubmission.

21 DR. GUTMAN: Yeah, it does impact, sure.

22 CHAIRMAN WILSON: Okay. We have a motion  
23 for approvable with conditions.

24 Yeah, go ahead.

25 DR. KOUTSKY: I don't know what can be

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1 considered a condition. So I suggest these here if  
2 they're inappropriate.

3 One would be a condition that there is  
4 educational materials to go along with the tests, and  
5 if there's some way that it can be distributed to the  
6 users and not just to the labs.

7 And the second is -- and I guess this is  
8 where I would see the need for more information on  
9 clinical use and clinical outcomes, is to do some post  
10 marketing surveillance on how the test is being used  
11 and what impact it has on clinical outcomes.

12 CHAIRMAN WILSON: Okay. Let me summarize  
13 then the current motion on the table is for approvable  
14 with conditions, now being four conditions.

15 First is specific recommendations for  
16 using the test clinically.

17 The second is a demonstration that those  
18 recommendations will have a positive impact on  
19 clinical outcomes.

20 The third recommendation is that education  
21 materials, the company would test both in -- our  
22 educational materials both in the laboratories and for  
23 users.

24 And the fourth recommendation would be  
25 that there be post marketing surveillance to assess

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1 the impact on clinical outcomes.

2 Dr. Reller?

3 DR. RELLER: I think the first two  
4 conditions that you mentioned or clarify if that's Dr.  
5 Berry's intent that those were premarketing.

6 CHAIRMAN WILSON: Is that correct, Dr.  
7 Berry?

8 DR. BERRY: Yes.

9 CHAIRMAN WILSON: Okay. Are there any  
10 further comments or questions, points that need to be  
11 clarified?

12 Dr. Nolte.

13 DR. NOLTE: Yeah, the point I brought up  
14 earlier in terms of the semi-quantitative aspect of  
15 this test and the concerns I have about should this  
16 test become widely applied to the 55 million or so PAP  
17 smears that are going to be done on women that have  
18 those PAP smears.

19 The issues about the way that the test is  
20 designed with a single sort of cutoff point may  
21 intensify problems, low positives, false positives,  
22 whatever you want to call them, that the company if  
23 they have the data in terms of the readout, the  
24 relative light unit data, to see if there's anything  
25 that could be done to establish a gray zone or a

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1 situation that might prevent calling low level  
2 positives positive when, in fact, they are negative.

3 In this test, the cutoff is 342 and the  
4 value is 341. It's a negative. If it's 343, it's a  
5 positive, and that's okay, I think, with the current  
6 application because you're enriching the patients you  
7 test for the ones that have the disease.

8 But now if this goes through, and we're  
9 talking about it as a screening test, I'm really  
10 uncomfortable with the assay design or at least the  
11 interpretation of the assay.

12 So I'd like to talk about that as a  
13 condition for approval.

14 CHAIRMAN WILSON: Dr. Birdsong.

15 DR. BIRDSONG: I would like to just state  
16 I agree with the other Panel member who spoke about  
17 the need for educational material as far as clinicians  
18 and patients. I'm sure if it goes through, the  
19 company is going to at the very least attempt to  
20 educate the labs just as a part of marketing, but it's  
21 important for the clinicians to be educated as to the  
22 implications of HPV positive, PAP negative patients.

23 And that's walking a fine line because, as  
24 I said earlier, not going back on what I said, but  
25 it's not the company's role to actually develop

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1 guidelines. This is something new and, you know,  
2 fraught with potential problems in terms of its social  
3 implications.

4 And, you know, I don't think that can be  
5 overstated. It's not as important as preventing  
6 cancer, again, but it is very important and, you know,  
7 I don't think it would be a good thing to under  
8 estimate the importance of that.

9 So education is important, and in the  
10 absence of -- hopefully the professional societies  
11 would pick up the ball and, you know, develop some  
12 more specific guidelines, but in their absence at  
13 least some suggestion as to how the various possible  
14 outcomes of this proposal, of the proposed test would  
15 be used, I think, would be helpful.

16 CHAIRMAN WILSON: Dr. Koutsky.

17 DR. KOUTSKY: I just wanted to comment on  
18 the question about roles and about -- perhaps can  
19 Digene comment on this?

20 All right. Limit to my experience.

21 I think for a lot of infectious diseases,  
22 you know, certainly the amount of virus demonstrated  
23 is very important in the disease causation. Probably  
24 for the infection and maybe early on in establishing  
25 an SIL level is important, but I think the data pretty

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1 much show within the range of what we can look at  
2 quantitatively, it doesn't appear to be important with  
3 salient free and cancers.

4 But that's not giving you what you might  
5 want because probably you just need a small group of  
6 about one cell infected. That least to, you know, a  
7 clone that becomes cancer. So it's not that  
8 quantitative information doesn't appear to be useful.

9 DR. NOLTE: And I understand that, and I  
10 understand from the literature that was in the packet  
11 that there's not a tight correlation between disease  
12 state and viral load, if you will.

13 And there are all sorts of problems, as  
14 Dr. Unger pointed out, in terms of using this test in  
15 a quantitative fashion. There's no denominator  
16 essentially. It's all dependent upon the amount of  
17 cellular material you get.

18 But what I am concerned about is those  
19 values that hover around the cutoff in this asset, and  
20 I'm wondering whether a look at the large data set  
21 that they have might help define an area that's  
22 recalling the question, some of the positive results.

23 CHAIRMAN WILSON: Dr. Durack.

24 DR. DURACK: I'd just like to reinforce  
25 briefly for the sake of clarity that the requirement

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1 to demonstrate a positive impact on clinical outcomes  
2 would require a very long study, certainly a long  
3 study.

4 And in view of the number of years that  
5 might be required, it might be considered unduly  
6 burdensome.

7 DR. RELLER: May I comment? I wasn't  
8 thinking of a long-term study. I was thinking mostly  
9 of a reanalysis of the data that they have, especially  
10 the longitudinal data. There could be some modeling  
11 of things that we know about the disease and detection  
12 of the disease.

13 I wasn't thinking of a long-term study.  
14 Whether they can do it on the basis of the data that  
15 they have is another matter.

16 CHAIRMAN WILSON: Thank you. I'd like to  
17 at this point review the motion that's on the table.  
18 this is for a motion of approval with conditions and,  
19 I think, five conditions.

20 DR. BERRY: May I just -- the fifth  
21 condition, I think, could be subsumed into the  
22 demonstration or into how to use the test. So if we  
23 interpret the test broadly, I think that would  
24 accommodate Dr. Nolte's point.

25 Dr. Nolte, are you willing to accept that?

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1 DR. NOLTE: I'm not sure I'm following  
2 what you're saying.

3 DR. BERRY: Well, the first condition that  
4 I had was using the test, that they should tell us how  
5 we should use the test, and interpreting that broadly,  
6 if the test is just a little bit above the cutoff or  
7 a little bit below the cutoff, then that's something  
8 that they should address.

9 DR. NOLTE: Fine. I mean --

10 DR. BERRY: See, I'm a little bit worried  
11 about, you know, having lots of conditions and then  
12 people voting against because there are so many  
13 conditions.

14 DR. FELIX: A procedural question.

15 CHAIRMAN WILSON: Yes.

16 DR. FELIX: Do we vote on each individual?

17 CHAIRMAN WILSON: No, we vote on the  
18 motion. We have to agree on what the recommendations  
19 will be. Then we would need a second, and then we  
20 vote on the full motion.

21 Okay. So, Dr. Nolte, are you agreeable to  
22 what was suggested?

23 DR. NOLTE: Sure, as long we're clear  
24 about that the quantitative aspects, semi-quantitative  
25 aspect of this assay needs to be examined. The data

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1 needs to be examined to see if there's any way to  
2 improve the specificity as it's applied to allow  
3 prevalent populations. That's my point.

4 CHAIRMAN WILSON: Okay. So let me repeat  
5 then. The motion is for approval with conditions,  
6 there being the first condition, specific  
7 recommendations for using the test clinically, and  
8 this would include Dr. Nolte's concerns about the  
9 interpretive criteria for the gray zone;

10 The second recommendation being a  
11 demonstration that these recommendations will have a  
12 positive impact on clinical outcomes.

13 The third recommendation is that  
14 educational materials accompany the test, and these  
15 are both laboratory as well as clinical users.

16 And the fourth recommendation is that post  
17 marketing surveillance be undertaken that would have  
18 an assessment on the impact on outcomes.

19 Okay. We have a motion for approval with  
20 conditions. I do not yet have a second on that  
21 motion.

22 Dr. Reller?

23 DR. RELLE: I will second it, but I want  
24 to make sure that we understand that at least the  
25 first two are premarketing.

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1 CHAIRMAN WILSON: Yes.

2 DR. RELLER: I'll second that motion.

3 CHAIRMAN WILSON: Good. Then we'll vote  
4 on that. Then we'll come back to the individual  
5 recommendations and go around the table again.

6 Dr. Reller?

7 DR. RELLER: Yes.

8 CHAIRMAN WILSON: Dr. Berry.

9 PARTICIPANT: Excuse me. Don --

10 CHAIRMAN WILSON: Yes.

11 PARTICIPANT: -- here, Deputy Division  
12 Director.

13 I think you need to vote on each of the  
14 conditions first and then make a final vote on all of  
15 them.

16 CHAIRMAN WILSON: Okay. that's fine.  
17 Thank you.

18 Let's go around then on the first. It's  
19 the premarket recommendation that there be specific  
20 recommendations for using the test clinically.

21 DR. RELLER: Yes.

22 CHAIRMAN WILSON: Dr. Berry?

23 DR. BERRY: yes.

24 CHAIRMAN WILSON: Dr. Janosky.

25 DR. JANOSKY: Yes.

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1 DR. FELIX: No.

2 CHAIRMAN WILSON: Dr. Koutsky?

3 DR. KOUTSKY: No.

4 CHAIRMAN WILSON: Dr. Beavis.

5 DR. BEAVIS: Yes.

6 CHAIRMAN WILSON: Dr. Nolte?

7 DR. NOLTE: No.

8 CHAIRMAN WILSON: And Dr. Birdsong.

9 DR. BIRDSONG: No.

10 CHAIRMAN WILSON: Okay. We have a tie

11 vote, four to four. I'm just doing the tally.

12 Okay. We do have a tie vote. It's four

13 to four, which leaves the tie breaking vote to me as

14 the Panel Chair. I'm going to vote yet.

15 Okay. The second recommendation is,

16 again, a premarket recommendation that the specific

17 recommendations for using the test clinically

18 demonstrate that the recommendations will have a

19 positive impact on clinical outcomes.

20 And we'll go around again, starting with

21 Dr. Reller.

22 DR. RELER: I will vote yes to this, but

23 I think that there would be considerable work, exactly

24 what we mean by positive outcome.

25 CHAIRMAN WILSON: Dr. Berry.

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1 DR. BERRY: Yes.

2 CHAIRMAN WILSON: Dr. Janosky.

3 DR. JANOSKY: Yes.

4 CHAIRMAN WILSON: Dr. Felix.

5 DR. FELIX: No.

6 CHAIRMAN WILSON: Dr. Koutsky.

7 DR. KOUTSKY: No.

8 CHAIRMAN WILSON: Dr. Beavis.

9 DR. BEAVIS: Yes.

10 CHAIRMAN WILSON: Dr. Nolte.

11 DR. NOLTE: No.

12 CHAIRMAN WILSON: And Dr. Birdsong.

13 DR. BIRDSONG: No.

14 CHAIRMAN WILSON: Okay. Again, we have a

15 tie vote.

16 (Laughter.)

17 CHAIRMAN WILSON: Leaving the tie

18 breaking vote to me once again, and on this one I'm

19 going to vote yes as well.

20 Okay. The third recommendation is that

21 educational materials accompany the test or at least

22 be available both to the laboratories, as well as the

23 clinical users of the test.

24 Once again starting with Dr. Reller.

25 DR. RELER: Yes.

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1 CHAIRMAN WILSON: Dr. Berry.

2 DR. BERRY: Yes.

3 CHAIRMAN WILSON: Dr. Janosky.

4 DR. JANOSKY: Yes.

5 CHAIRMAN WILSON: Dr. Felix.

6 DR. FELIX: Yes.

7 CHAIRMAN WILSON: Dr. Koutsky.

8 DR. KOUTSKY: Yes.

9 CHAIRMAN WILSON: Dr. Beavis.

10 DR. BEAVIS: Yes.

11 CHAIRMAN WILSON: Dr. Nolte.

12 DR. NOLTE: Yes.

13 CHAIRMAN WILSON: And Dr. Birdsong.

14 DR. BIRDSONG: Yes.

15 CHAIRMAN WILSON: Okay. That motion  
16 passed. It carried unanimously.

17 Given the last recommendation is that post  
18 marketing surveillance be undertaken that will assess  
19 the impact of the clinical outcomes, on clinical  
20 outcomes.

21 We'll begin with Dr. Reller again.

22 DR. RELER: Yes.

23 CHAIRMAN WILSON: Dr. Berry.

24 DR. BERRY: Yes.

25 CHAIRMAN WILSON: Dr. Janosky.

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1 DR. JANOSKY: Yes.

2 CHAIRMAN WILSON: Dr. Felix.

3 DR. FELIX: No.

4 CHAIRMAN WILSON: Dr. Koutsky.

5 DR. KOUTSKY: Yes.

6 CHAIRMAN WILSON: Dr. Beavis.

7 DR. BEAVIS: Yes.

8 CHAIRMAN WILSON: Dr. Nolte.

9 DR. NOLTE: No.

10 CHAIRMAN WILSON: And Dr. Birdsong.

11 DR. BIRDSONG: I'm going to say yes. I'm  
12 mixed on that one actually.

13 CHAIRMAN WILSON: Okay. That passes.  
14 That part of the motion carries by six to two.

15 DR. FELIX: Okay. That last vote, I think  
16 a lot of people voted in a vacuum. So the panelists  
17 have approved now premarket approved that it's going  
18 to be effective, as well as post market surveillance?  
19 is that the intention of the panel, that both be --

20 CHAIRMAN WILSON: We have approved --

21 DR. FELIX: -- put upon the company?

22 CHAIRMAN WILSON: -- the individual  
23 recommendations, but we have yet to put all of those  
24 together under the overall motion, to vote on that.

25 DR. FELIX: Okay. I see. I guess

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1 everybody was aware that --

2 CHAIRMAN WILSON: Right.

3 DR. FELIX: -- both of those existed.

4 CHAIRMAN WILSON: Right.

5 DR. BERRY: Just to clarify, my impression  
6 was that the original -- that the first showing that  
7 it will have an impact on clinical outcome was the  
8 premarket, the preapproval was based on data. The  
9 actual impact on clinical practice may vary  
10 substantially from that, and my understanding of the  
11 motion was to survey that, to see what it was.

12 Laura, is that right?

13 DR. KOUTSKY: Right. That one success is  
14 being used, that you get an understanding that it's up  
15 to the company to provide some information on how it's  
16 being used, what effect it's having on clinical  
17 practice and outcomes.

18 DR. BERRY: Right. So it's not at all  
19 contradictory. They're actually supportive of each  
20 other.

21 CHAIRMAN WILSON: Okay. So at this point  
22 then the motion is on the table. It's for approvable  
23 with conditions, with the four conditions we just  
24 voted on. So we have a motion. I need a second on  
25 that motion.

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1 DR. RELLER: I'll second the motion.

2 CHAIRMAN WILSON: Okay. We have a motion  
3 and a second. Is there any further discussion or does  
4 anyone need any other points clarified?

5 DR. NOLTE: Would you restate the  
6 conditions, please?

7 CHAIRMAN WILSON: Okay. I will restate  
8 the motion with the conditions.

9 The motion is approvable with conditions,  
10 there being four conditions.

11 The first of these is that there be on a  
12 premarket basis specific recommendations for using the  
13 test clinically.

14 The second condition, again, on a  
15 premarket basis, that there be a demonstration that  
16 these recommendations will have a positive impact on  
17 clinical outcomes.

18 The third conditions is that education  
19 materials accompany the test, materials to be provided  
20 both to the laboratories as well as clinical users.

21 And the fourth recommendation is that  
22 there be post marketing surveillance to assess the  
23 impact on clinical outcomes.

24 Dr. Birdsong.

25 DR. BIRDSONG: Can I ask for a

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1 clarification on the condition, the premarket  
2 condition, the positive impact on clinical outcomes?  
3 Is that to be an additional study or based on analysis  
4 of already existing data?

5 CHAIRMAN WILSON: I think as Dr. Gutman  
6 has stated, that that's something that the FDA can  
7 work on as to what the best approach is.

8 Steve, do you have any specific comments  
9 on that?

10 DR. GUTMAN: No.

11 CHAIRMAN WILSON: Okay. So we have a  
12 motion and a second. I'd like to take the vote at  
13 this time. We'll begin again with Dr. Reller.

14 DR. RELER: Yes.

15 CHAIRMAN WILSON: Dr. Berry.

16 DR. BERRY: Yes.

17 CHAIRMAN WILSON: Dr. Janosky.

18 DR. JANOSKY: Yes.

19 CHAIRMAN WILSON: Dr. Felix.

20 DR. FELIX: No.

21 CHAIRMAN WILSON: Dr. Koutsky.

22 DR. KOUTSKY: Yes.

23 CHAIRMAN WILSON: Dr. Beavis.

24 DR. BEAVIS: Yes.

25 CHAIRMAN WILSON: Dr. Nolte.

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1 DR. NOLTE: Yes.

2 CHAIRMAN WILSON: And Dr. Birdsong.

3 DR. BIRDSONG: No.

4 CHAIRMAN WILSON: The motion then carries  
5 by a vote of six to two.

6 At this point I'd like to go around and  
7 ask each of the panel members once again to state  
8 their reasoning and the thoughts behind their vote.

9 We'll begin with Dr. Reller.

10 DR. RELLER: I think we have an approved  
11 good test for the detection of HPV DNA. How to use  
12 that appropriately in actual practice in conjunction  
13 with the PAP smear we do not have now, and I think we  
14 need it to use the test safely and effectively in  
15 patients who could potentially benefit.

16 And until those things are delineated in  
17 these conditions, I do not think the test should be  
18 approved.

19 CHAIRMAN WILSON: Dr. Berry.

20 DR. BERRY: I have nothing further to add.

21 CHAIRMAN WILSON: Dr. Janosky.

22 DR. JANOSKY: It's my understanding is  
23 that we were to vote on safety and effectiveness for  
24 the indication for use, and it seems like what we  
25 voted on was safety and effectiveness, but not for any

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1 specific indication for use.

2 Whether you call that a not approvable or  
3 approvable with these conditions that we had outlined,  
4 that doesn't seem to clear to me. So I can safely say  
5 that I voted on safety and effectiveness, but no  
6 specific indication for use. Hopefully those  
7 premarketing studies will tell us what those  
8 indications really should be.

9 CHAIRMAN WILSON: Thank you.

10 Dr. Felix.

11 DR. FELIX: I voted no because I could not  
12 agree with the conditions of the approval. I could  
13 not disagree with the data presented for women age  
14 over 40 as an indication. So that the first condition  
15 was providing an indication for use in screening in  
16 women over 30. I felt that that was a -- that they  
17 had proven that and think that both a premarket and a  
18 post market study are unduly burdensome on the  
19 sponsor.

20 CHAIRMAN WILSON: Thank you.

21 Dr. Koutsky.

22 DR. KOUTSKY: I voted yes because I think  
23 the educational materials and the post marketing  
24 surveillance and impact of outcomes are important, and  
25 that I can see that there are clinicians on the panel,

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1 that there was an interest in having specific  
2 recommendations made by Digene. I do have a problem  
3 with the premarketing additional information that was  
4 requested. I'm sure that the FDA and Digene can work  
5 that out.

6 CHAIRMAN WILSON: Thank you.

7 Dr. Beavis.

8 DR. BEAVIS: I voted in favor of the  
9 motion because I wanted to make sure that the way this  
10 test would be used is outlined before it hits the  
11 market.

12 CHAIRMAN WILSON: Dr. Nolte.

13 DR. NOLTE: I voted in favor of the  
14 resolution. I guess I'm learning how to play  
15 politics. Most of the amendments, I think, are a  
16 little burdensome, but I think basically the test has  
17 value, and I'd like to see it get out there for that  
18 purpose.

19 CHAIRMAN WILSON: Thank you.

20 And Dr. Birdsong.

21 DR. BIRDSONG: I may be learning to play  
22 politics a little bit also, but I voted against it for  
23 a reason similar to Dr. Felix. I think the condition  
24 for premarket demonstration of effectiveness is not  
25 necessary, and specifically I don't think it belongs

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1 there, and were that condition not there, I would have  
2 voted yes.

3 And second, you know, as I stated earlier,  
4 I think the stated indication of screening for  
5 cervical cancer in women over 30, screening is an  
6 indication, and I think that's stated clearly, and it  
7 doesn't need further modification.

8 CHAIRMAN WILSON: Thank you.

9 As I did register two votes on the  
10 recommendations, I'm obliged as well to comment on my  
11 thinking.

12 I concur with the comments of Drs. Reller  
13 and Berry in that I believe that there needs to be  
14 very clear specificity about what a clinician on the  
15 first line is going to do with one of these test  
16 results, even in the absence of guidelines from ACOG  
17 or what other body is out there.

18 There needs to be specific clinical  
19 guidelines that providers that get a result know what  
20 to do with those results.

21 Okay. That concludes the business today.  
22 I would like to thank all of the members of the panel  
23 who traveled here today, regular panel members as well  
24 as consultants and guests.

25 I'd also like to thank Digene for their

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1 presentation, as well as the FDA.

2 Thank you, and the meeting is adjourned.

3 (Whereupon, at 4:23 p.m., the Panel  
4 meeting was concluded.)

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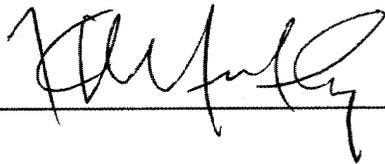
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