

in favor, I could imagine that when the devil is put in the details that I would vote in favor on the basis of the information that was shown today.

DR. GUTMAN: Would the panel's opinion be changed if, in fact, we had access to some or all of the raw or the line data?

DR. DURACK: I would just give a general comment. I think it is essential to have access to the underlying data, that there shouldn't be any innate bias against using x U.S. data, but it should be comparable populations. And that has got to be very carefully analyzed that they are comparable. The study conditions should meet our criteria.

Given those two, then I think we can place a lot of confidence in the overseas data. Likewise, if the populations are not comparable, or if the conditions are up to our standards, then--

DR. WILSON: Dr. Brown?

DR. BROWN: I would just emphasize, though, I think because some of the issues that one of the other people raised, it may not be related to doing the test, itself, the technical, but some of the quality sociological issues I think do need to be addressed in the U.S. populations. I think there are some studies that already have been done that we didn't hear the data about that we could hear, even if it is small numbers, that might address

some of those issues better.

So I would encourage the raw data from those studies that already have been completed and others that may be completed in the near future to be presented, also.

DR. FELIX: I think that the problem that I have and, although I think the data is extremely promising and I, personally, have believed that the test is a good test and it is a good strategy, I have the problem with looking at previous published results or studies in that some studies that were not presented to the panel in this instance don't quite reflect the same optimistic results.

So if we are going to base our decision on previous published experience, I think we will have to see all of it, not just part of it that gets presented to us. I am not saying that--again, I agree with the comment that, as long as the populations are comparable, and the methodology is what we would undertake, then I would be willing to accept positive results and look at the data favorably.

But, again, I would not do so without an analysis of all of the data that is available.

Open Public Hearing

DR. WILSON: Before we move on to the final portion of the meeting, we are required to have another open public hearing. So, at this time, we will accept comments from any member of the public. If you would just please

come forward and identify yourself. We would ask that you limit your comment to two minutes.

DR. SCHIFFMAN: I am Mark Schiffman. I am in charge of HPV and cervical-cancer natural-history studies at NCI. I have no conflicts. It disturbed me that there was a notion that there was a complete data representation here today. I don't know who was responsible for making that, but it may be a pivotal study that we are doing that--we have a ten-year study underway of 24,000 women in Portland, Oregon.

The endpoint is either histologically confirmed or cytologically verified CIN 2,3. It is infrequently screened women. And, so far, I can report, though, the analysis is not finished, that there is complete protection against any CIN 2,3, at least for the first two-and-a-half years following a double negative of a Pap-negative HPV-oncogenic negative.

Colposcopy is not a gold standard. It is definitely confirmed that cytology can find lesions that are missed by colposcopy. That is definitely true and I comment Belinson's work on that. Also, HPV in our work, finds lesions that are missed by colposcopy and are only confirmed after that HPV has confirmed that colposcopy has missed them.

So, we find very high absolute and relative risks

of HPV-positivity so that women who are positive either for HPV or for cytology have much, much higher absolute risks over time than women who are double negative who, in fact, have no risk for the first two-and-a-half years and then incrementally the protection fades away as time goes on.

So I urge you keep an open mind. I hadn't planned on testifying or doing anything, but it disturbed me that it got to be at the point where people were talking that it was a closed case or something.

DR. WILSON: Thank you.

Are there any other comments?

DR. FELIX: I have a question about that study, Dr. Schiffman. In that study that you just mentioned, you said that there was a complete protection. Did they biopsy women who were double-negative?

DR. SCHIFFMAN: No. We are using follow up. In other words, people come back and if there is any cytology suggestion CIN 2,3, then they are biopsied. Of, in fact, if it is CIN 1, they are biopsied.

DR. FELIX: So, according to that strategy, no histologic evidence is present in the double-negative group.

DR. SCHIFFMAN: Right. All I can tell you is that there is no--I can tell you that the relative risk is astronomical.

DR. COX: I just have a couple of comments. Evan

said that we really should apply this to all age groups because we can't keep OB-GYNs or other clinicians from using it in all age-group levels. I think we have seen great confusion a few years ago about ASCUS and HPV use. With education, we have been able to really change that course. I think it is possible to educate, educate, educate clinicians to get them to understand the use of this.

Penny Hitchcock said if we could ordain that HPV plus Pap would be done only and 30 and above, then much of her talk would be moot and her concerns would be moot. I agree that concerns can be applied if we use it under the age of 30

Again, my reply to her would be I believe, truly, that with education, we can make this an issue that is a non-issue for clinicians. I agree there is a learning curve with everything we do but much we do in medicine, there is much change in technology with medicine. There is a learning curve that we have to overcome.

I don't think that that is any reason to deter the use of this test in the future in the manner in which we are describing. In terms of biopsy and double-negative women, I think that puts a huge burden on the study in this country to get women to agree to this. I don't believe I have heard from any women here yet say that it doesn't hurt to get a cervical biopsy. The people that have commented on these

painless biopsy procedures have all been men.

I think that there is a wealth of data out there which gives us great reassurance that the potential for--I won't say a wealth, but several studies, long-term follow-up studies, that negative-negative really does not result in any detection of disease and long-term follow up.

Mark mentioned his study and the studies by Nobbenhuis and Walboomers in the Netherlands are a really good example. So I would think that would could do studies without biopsy in normal women.

Thank you.

DR. WILSON: Thank you.

Are there any other comments? If not, the public session is closed.

Final Recommendations

At this point in the final part of the meeting, what I would like to do is go around and have each of the panelists give any final comments they have, any suggestions they might have, guidance for the FDA. We didn't spend any time on the question about home-collection devices but if anyone has any particular thoughts about that, we would like to hear those at this time.

Mr. Reynolds, would you like to go first

MR. REYNOLDS: I have already commented previously about my feeling about any sort of home collection or

alternative devices. If that would, in any way, help to address these populations that are not currently being screened then, perhaps, it is some use.

DR. WILSON: Dr. Felix?

DR. FELIX: I have nothing further to add.

DR. WILSON: Dr. Myers.

DR. MYERS: The only thing I would like to do is just reemphasize that we really need good quality-of-life data on all of the outcomes of these different strategies so that we can really intelligently compare them.

DR. WILSON: Dr. Reller?

DR. RELER: Nothing.

DR. WILSON: Dr. Hammerschlag?

DR. HAMMERSCHLAG: Nothing.

DR. WILSON: Dr. Weinstein?

DR. WEINSTEIN: Nothing.

DR. WILSON: Dr. Tuazon?

DR. TUAZON: Nothing.

DR. WILSON: Dr. Brown?

DR. BROWN: No.

DR. WILSON: Dr. Durack?

DR. DURACK: Just another comment on the home-collection issue, very important, and, in a way, it is a separate issue. We have got the issue of the test and there is an overlap. But there is also the separate issue of

home-collection devices and whether they will assist not just in this application but in other ways, as well.

So I think it is certainly deserving of attention. Maybe we have got to be careful not to confuse the two or at least be careful about what the overlap is.

DR. WILSON: Thank you. If there are no further comments, at this point, Dr. Mirhashemi did you want to make any final comments?

DR. MIRHASHEMI: No; I abstain.

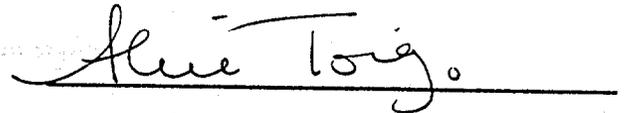
DR. WILSON: At this point, I would like to thank the members of the public and industry who took time to be here today. I would like to thank all the members of the panel, particularly our guest members who came in for today, members of the FDA in their help preparing all of the data and, of course, as always, to Ms. Poole for all the tremendous amount of work she does and all of her help.

The meeting is adjourned.

[Whereupon, at 4:00 p.m., the meeting was adjourned.]

CERTIFICATE

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