

## U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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## PUBLIC HEALTH SERVICE

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FOOD AND DRUG ADMINISTRATION  
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH  
IMMUNOLOGY DEVICES PANEL MEETING

+ + + + +

MONDAY

DECEMBER 13, 1999

+ + + + +

The meeting took place in Conference Room 020B, 9200 Corporate Boulevard, Rockville, Maryland, at 10:00 a.m., Charles T. Ladoulis, M.D., Chairperson, presiding.

PRESENT:

CHARLES T. LADOULIS, M.D.	Chairperson
LOUISE E. MAGRUDER	Executive Secretary
BETTS CARPENTER, M.D., Ph.D.	Voting Member
GLEN L. HORTIN, M.D., Ph.D.	Voting Member
MARY M. KEMENY, M.D.	Voting Member
DANIEL P. PETRYLAK, M.D.	Voting Member
SHEILA E. TAUBE, Ph.D.	Voting Member
DONALD A. BERRY, Ph.D.,	Temp. Voting Member
ROBERT R. DILORETO, M.D.	Voting Member
BARNARESE P. WHEATLEY, M.P.H.	Consumer Rep.
ERIKA B. AMMIRATI, R.A.C.	Industry Rep.
STEVEN GUTMAN, M.D.	FDA Representative

ALSO PRESENT:

MELODIE R. DOMURAD, Ph.D.	Sponsor Rep.
S. BRUCE MALKOWICZ, M.D.	Sponsor Rep.
JOSEPH BRIGGMAN, Ph.D.	Sponsor Rep.
NINA CHACE	FDA Representative
TOM GROSS, M.D.	Sponsor Rep.
GREG CAMPBELL, Ph.D.	Sponsor Rep.

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**Adjournment****NEAL R. GROSS**

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P-R-O-C-E-E-D-I-N-G-S

(10:03 a.m.)

1  
2  
3 CHAIRMAN LADOULIS: We will now have the  
4 open session. And so, Louise, you are going to make  
5 some announcements before everyone before from Louise  
6 Magruder, okay.

7 MS. MAGRUDER: Good morning. Welcome to  
8 today's panel meeting. I'm Louise Magruder, Executive  
9 Secretary of the Immunology Devices Panel of the  
10 Medical Devices Advisory Panel Meeting. And I'm going  
11 to ask the Panel Members to please introduce  
12 themselves starting with our Chairperson.

13 CHAIRMAN LADOULIS: Charles Ladoulis,  
14 Chair of the Immunology Devices Panel. And Dr. Hank,  
15 Dr. Henry Hamburger will not be able to attend today.

16 DR. HORTIN: Glen Hortin, I'm a Panel  
17 Member and I'm in the Clinical Pathology Department at  
18 NIH.

19 DR. TAUBE: Sheila Taube, I'm the  
20 Associate Director of the Cancer Diagnosis Program at  
21 the National Cancer Institute.

22 DR. GUTMAN: I'm Steve Gutman, I'm the  
23 Director of the Division of Clinical Laboratory  
24 Devices, FDA.

25 MS. WHEATLEY: My name is Bonnie Wheatley

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1 and I'm the Director of the Breast Cancer Early  
2 Detection Program and I'm the Consumer Representative  
3 here.

4 MS. AMMIRATI: I'm Erika Ammirati,  
5 Industry Representative to this Panel and do my own  
6 consulting.

7 DR. BERRY: I'm Don Berry, Chair of  
8 Biostatistics at MD Anderson Cancer Center in Houston.

9 DR. CARPENTER: Betts Carpenter, I'm a  
10 Pathologist, Vice Chairman and Professor at Marshall  
11 University in Huntington, West Virginia.

12 DR. PETRYLAK: I'm Daniel Petrylak, I'm a  
13 Medical Oncologist and Director of GU Oncology at  
14 Columbia Presbyterian in New York.

15 DR. KEMENY: I'm Margaret Kemeny, I'm the  
16 Head of Surgical Oncology at SUNY Stony Brook and a  
17 Panel Member.

18 DR. DILORETO: Robert DiLoreto, practicing  
19 Urologist, Michigan Institute of Urology, Detroit,  
20 Michigan.

21 MS. MAGRUDER: The Immunology Devices  
22 Panel last met on November the 9th, 1999. The Panel  
23 discussed, made recommendations and voted approvable  
24 with conditions on a pre-market approval application  
25 for the Vysis PathVysion HER-2 neu, HER-2 DNA Probe

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1 Kit, designed to detect amplification of the HER-2  
2 gene via fluorescence in situ hybridization in  
3 paraffin embedded specimens from subjects with no  
4 positive Stage 2 breast cancer.

5 The Immunology Devices Panel Meeting dates  
6 for next year, the year 2000, are tentatively  
7 scheduled for March 17th, June 16th, September 15th  
8 and December 8th. Dr. Steve Gutman, Director of the  
9 Division of Clinical Laboratory Devices will make a  
10 presentation.

11 DR. GUTMAN: Good morning. One of the  
12 most important resources that the FDA has to draw on  
13 in its review of the work product that we passionately  
14 know and love is this Advisory Panel. And today marks  
15 a milestone in that three of the pillars of this Panel  
16 have completed four years of really excellent service  
17 and I'd like to recognize those individuals. Those  
18 three individuals are Dr. Kemeny, Dr. Taube and Dr.  
19 Ladoulis.

20 And all of them, as those you who have  
21 been following the life of this panel know, have been  
22 active and vigorous and wonderful participants and  
23 have helped us through a whole host of complex and  
24 fascinating products and problems. They've done good  
25 work and what I have is a letter from our

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1 Commissioner, Dr. Henney, and a plaque signed by our  
2 new Center Director, Dr. Feigal, and Dr. Henney as  
3 well. And I'd like to hand those out to these three  
4 folks.

5 There is no reward for good work and the  
6 bottom line is you can never escape, you can never  
7 escape the clutches of the FDA. It was our intention  
8 to take all three of these folks and roll them over  
9 onto our consultative list, so we do hope that there  
10 will be a revisit when appropriate products do come  
11 up. And I'd like to offer them a hand of applause.

12 (Applause.)

13 MS. MAGRUDER: And now Dr. Tom Gross,  
14 Director of the Division of Post-Market Surveillance,  
15 will give a presentation on post-market evaluation at  
16 CDRH.

17 DR. GROSS: Good morning. My name is Tom  
18 Gross and I'm the Director of the Division Post-Market  
19 Surveillance here at CDRH. And I'd like to take a few  
20 minutes of your time this morning to talk to you about  
21 post-market evaluation here at the Center. We think  
22 it's important that the Advisory Panels are aware of  
23 post-market programs and activities since these may  
24 directly relate to your deliberations about a  
25 product's safety and effectiveness.

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1           Now the objectives of the presentation are  
2 three-fold. One, to describe a few of the key methods  
3 of device post-market evaluation, present challenges  
4 in accomplishing post-market evaluation and describe  
5 the pivotal role that Advisory Panels can play in this  
6 arena.

7           Now this slide entitled, From Design to  
8 Obsolescence, makes three key points. One is it  
9 depicts the natural history of devices from design,  
10 lab bench testing, clinical testing, FDA review and  
11 importantly, post-market evaluation.

12           Two, it depicts the continual feedback  
13 loops throughout this process leading to continual  
14 product improvement. We think that post-market  
15 evaluation has an important part to play in this  
16 process and the remainder of this talk will focus on  
17 three key programs within post-market evaluation, the  
18 MDR Program, Section 522, known as post-market  
19 surveillance studies and are conditions of approval  
20 studies under our PMA authority.

21           Now the third point that this slide makes  
22 is that the clinical community, and importantly the  
23 Advisory Panels, have a key part to play in this  
24 process of continual product improvement. Now we all  
25 know as products are released into the market place,

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1 questions or potential public health concern can arise  
2 in the post-market period. There could be issues  
3 about a product's long-term safety, about performance  
4 of device and community practice as it moves outside  
5 the narrow confines of clinical trials.

6 The effects of changes in user's setting,  
7 say for instance in moving your product from  
8 professional to home use. The affects of incremental  
9 changes in technology can raise safety questions. And  
10 there may be concerns about adverse events of unusual  
11 patterns of adverse events.

12 Now let's focus on some of these programs  
13 that may address some of these public health  
14 questions. Beginning with the Medical Device  
15 Reporting Program or MDR. Now this is a nationwide  
16 passive surveillance system of voluntary and mandatory  
17 reports.

18 The voluntary part of this program began  
19 in 1973. The mandatory part in 1984, and currently  
20 manufacturers are required to report deaths and  
21 serious injuries to the FDA, if the device may have  
22 caused or contributed to the event. And they are also  
23 required to report malfunctions. All user facilities,  
24 most notably hospitals and nursing homes, must report  
25 deaths to the FDA and serious injuries to the

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1 manufacturer.

2 Now since the database inception in 1973,  
3 all tolled, we have slightly over one million reports  
4 in our database. Beginning in the early '90's and  
5 continuing today, we've received about 100,000 reports  
6 a year. The information is sent in on standardized  
7 reporting forms that collect information on device  
8 specifics, event descriptions, pertinent dates and  
9 patient characteristics.

10 Unfortunately, reports often have limited  
11 information, even basic demographic information such  
12 as age and gender is missing from a number of reports.

13 But nonetheless, it can provide critical signals to  
14 the FDA for further action.

15 Now what are some of the actions prompted  
16 by the MDR Program? A further follow up of MDR  
17 reports we may issue, directed inspections of  
18 manufacturers or user facilities. It may lead to  
19 produce injunctions or seizures, product recalls,  
20 patient/physician notification, such as the 1997  
21 Public Health Advisory on Antibody Testing for Lyme  
22 Disease.

23 And it may occasionally lead to additional  
24 post-market studies. Now if we call for additional  
25 post-market studies, we have two authorities we can

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1 rely on. One, Section 522 in FDAMA, better known as  
2 post-market surveillance, and the other under our PMA  
3 authority for post approval or condition of approval  
4 studies. Now Section 522 was originally mandated in  
5 SMDA in 1990, and it was changed significantly in  
6 FDAMA in 1997. The 1990 version had categories and  
7 lists of devices, such as cardiovascular devices, the  
8 manufacturers of which were required to do post-market  
9 studies regardless of whether they were pertinent  
10 public health questions.

11 The '97 version no longer had those  
12 categories and lists, but FDA still retains its  
13 discretionary authority in ordering manufacturers to  
14 do post-market studies if their device presents  
15 particular public health issues. Now our post-  
16 approval or condition of approval studies, refers to  
17 PMA products and is reserved strictly for PMA  
18 products. The Section 522 authority extends our  
19 coverage to Class 2 or 3, 510K products who's failure  
20 may present a public health problem.

21 Now both authorities are seen as a  
22 complement to our pre-market efforts in maintaining  
23 the safety and effectiveness of products in the  
24 marketplace. Now I'm implementing the FDAMA version  
25 of post-market surveillance studies. We publish

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1 criteria to help guide or considerations on when to  
2 impose post-market studies on these Class 2 and 3 510K  
3 products. A principle criterion is that there has to  
4 be a critical public health question to address. This  
5 can come from four cause issues, such as notable  
6 adverse events, concerns about new or expanded  
7 conditions of use.

8 Moving a product, let's say, from  
9 professional to home use. Concerns about evolutions  
10 of technology that raise safety issues. Another  
11 criterion has to do with consideration of other post-  
12 market strategies. Perhaps mandating a study is not  
13 the best strategy to address the public health  
14 question. Manufacturers often will voluntarily study  
15 the issue or we may gain information through  
16 inspections or some aspect of our quality systems reg.

17 Thirdly, if we do order the study, we  
18 should make sure that they are practical and feasible  
19 to conduct. We can get sufficient numbers of  
20 patients, sufficient numbers of interested physicians.

21 In a related item, how will the data be used. This  
22 is particularly important for rapid technologies in  
23 which by the time we get the data, they are obsolete.

24 And lastly, of course, is the priority of  
25 the study. And in this age of limited resources we

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1 have to prioritize our efforts. Now once we decide to  
2 impose a post-market study requirement, there are  
3 several design approaches to choose from, as  
4 represented here from least burdensome to most  
5 burdensome or less complicated. We should try to pick  
6 that design approach that is least burdensome and also  
7 best addresses the public health question of interest.

8 On the least burdensome end, we may ask  
9 for a detailed review of complaint history of the  
10 literature and non-clinical testing of the device.  
11 And then moving up the category of complexity, we may  
12 ultimately ask for case control studies in rarely  
13 randomized trials. Now we've experienced several  
14 frustrations in the post-market period in conducting  
15 post-market studies.

16 One is an issue of rapid evolution of  
17 technology, it may make studies obsolete. And we  
18 should be aware of that prior to entering into these  
19 studies.

20 There may be lack of incentives for the  
21 industry to do these studies. The industry may view  
22 these studies only as being the bearers of bad news,  
23 raising potential safety issues about their product  
24 and we need to change that paradigm and get industry  
25 interested in doing these studies. There may be a

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1 lack of interest in the clinical community if we're  
2 studying the chore technologies. And lastly, we need  
3 to have clearly specified public health questions.

4 Now what's the challenge to the Advisory  
5 Panel and really a challenge to us all is that when  
6 considering post-market studies, under whatever  
7 authority, we need to ensure that they are of primary  
8 importance, that they are practical and feasible and  
9 conducted in a timely fashion. We need to clearly  
10 specify the public health question and we need to not  
11 the clinical or regulatory relevance of answering the  
12 question, what will we do with the data?

13 Are the data there to show us that our  
14 post-market experience is similar to a pre-market  
15 experience? Are they there to address residual  
16 questions? And again, can they be gathered in a  
17 timely fashion? The last slide speaks to the future  
18 of MDR and post-market surveillance studies. With  
19 regard to medical device reporting, moving away from  
20 individual reporting of well-characterized events to  
21 summary reporting. It's a more efficient way to  
22 review these events.

23 We're working on a project to institute  
24 sentinel reporting, which is taking a cadre of  
25 hospitals, rather than the universe of hospitals and

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1 focusing on them as the reporting entity to ensure  
2 better quality and more timely reports. We're moving  
3 into the era of electronic data interchange and having  
4 these reports submitted electronically. We're  
5 integrating our efforts with a quality system  
6 regulation. And lastly, we're currently exchanging  
7 significant adverse event reports internationally.

8 On the post-market surveillance study  
9 side, again, I've mentioned the wide variety of study  
10 design approaches we have to choose from. We'd like  
11 to pursue more collaboration with industry and the  
12 clinical community and make use of other existing data  
13 sources. That concludes my talk and thank you very  
14 much.

15 MS. MAGRUDER: Thank you, Dr. Gross.

16 This panel is here today to discuss, make  
17 recommendations and vote on a pre-market approval  
18 application for an enzyme immuno assay for the in-  
19 vitro determination of a nuclear matrix protein NMP22  
20 in stabilized voided urine.

21 This test kit is indicated as an aid in  
22 the diagnosis of persons with symptoms or risk factors  
23 for transitional cell cancer of the bladder, and in  
24 the management of patients with transitional cell  
25 carcinoma of the bladder after surgical treatment to

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1 identify those patients with occult or rapidly  
2 reoccurring transitional cell carcinoma.

3 At this time, I will read into the record  
4 the waivers for the conflict of interest statement and  
5 temporary voting status. Immunology Devices Panel  
6 Meeting, December 13th, 1999, Conflict of Interest  
7 Statement. The following announcement addresses  
8 conflict of interest services associated with this  
9 meeting and is made part of the record to preclude  
10 even the appearance of an impropriety.

11 The conflict of interest statues prohibit  
12 special government employees from participating in  
13 matters that could affect their or their employees'  
14 financial interest. To determine if any conflict  
15 existed, the agency reviewed the submitted agenda and  
16 all financial interests reported by the Committee  
17 participants and has determined that no conflict  
18 exists. In the event the discussions involved any  
19 other products are firms not all ready on the agenda,  
20 for which an FDA participant has a financial interest.

21 The participant should excuse him or  
22 herself from such involvement and their exclusion will  
23 be noted for the record. With respect to all other  
24 participants, we ask in the interest of fairness, that  
25 all persons making statements or presentations

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1 disclose any current or previous financial involvement  
2 with any firm who's product they may wish to comment  
3 on. Appointment to temporary voting status. Pursuant  
4 to the authority granted under the Medical Devices  
5 Advisory Committee Charter, dated October 27th, 1990,  
6 and as amended August 18th, 1999, I appoint the  
7 following individuals as Voting Members of the  
8 Immunology Devices Panel for this meeting on December  
9 13th, 1999.

10 Dr. Donald H. Berry, Dr. Robert R.  
11 DiLoreto. For the record, these individuals are  
12 special government employees and consultants to this  
13 Panel or other Panels under the Medical Devices  
14 Advisory Committee. They have undergone the customary  
15 Conflict of Interest Review and have reviewed the  
16 material to be considered at this meeting. Signed,  
17 David W. Feigal, Director, Center for Devices and  
18 Radiological Health, dated November 22nd, 1999.

19 At this point, Dr. Ladoulis will open the  
20 floor for the open public session. I would like to  
21 note for the record that no one has contacted the  
22 agency with a request to speak.

23 Dr. Ladoulis.

24 CHAIRMAN LADOULIS: Yes. Are there any  
25 members of the audience in this open session who would

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1 like to make any comments or presentations at this  
2 time? The forum is open to the public.

3 (No response.)

4 CHAIRMAN LADOULIS: There being none, then  
5 I think that we can proceed to the next item on the  
6 agenda. The Sponsor's presentation originally is  
7 scheduled for 11:15, but if the Sponsor is prepared to  
8 begin, we can -- it's now almost 10:25, and we could  
9 begin that presentation. Oh, yes, the overhead  
10 projection. You'll be using the microphone at the  
11 stand?

12 DR. DOMURAD: Whichever you prefer.

13 MS. MAGRUDER: It doesn't matter.

14 CHAIRMAN LADOULIS: Either microphone will  
15 be recorded, that's fine. And while they're setting  
16 up, I just wanted to confirm that arrangements have  
17 been made for the, the overheads?

18 DR. DOMURAD: Yes, they have.

19 CHAIRMAN LADOULIS: Okay, so everything is  
20 satisfactory?

21 DR. DOMURAD: Ladies and gentleman of the  
22 Panel, Members of the Agency, thank you for your time  
23 and attention. Is that better, or is there too much  
24 feedback?

25 Thank you for your time and attention here

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1 today. The Matritech NMP22 Test Kit is an enzyme  
2 immuno assay for the in-vitro quantitative  
3 determination of the nuclear matrix protein, NMP22, in  
4 stabilized voided urine.

5 It was approved in July, 1996, as an aid  
6 in the management of patients with transitional cell  
7 carcinoma after surgical treatment to identify those  
8 patients with occult or rapidly recurring TCC. The  
9 cut off of ten units per mil was chosen for this  
10 indication as providing optimal sensitivity of 76  
11 percent and specificity of 74.2 percent in those  
12 patients who had had a prior bladder cancer in the  
13 first disease episode after transurethral resection of  
14 the bladder tumor.

15 Recurrence rates, actually back please.  
16 Recurrence rates of bladder cancer after a first tumor  
17 are as high as 80 percent due to changes in the  
18 bladder and therefore require frequent monitoring. We  
19 seek the new intended use as an aid in the diagnosis  
20 of persons with symptoms or risk factors for  
21 transitional cell cancer of the bladder. Matritech  
22 conducted performance characterization precision  
23 testing according to the NCCLS guidelines on a variety  
24 of mean concentrations.

25 The concentrations tested are seen here in

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1 the third column. They ranged from 6.3 at the lowest  
2 to 96.3. The CVs, seen near the end, were within  
3 acceptable range. Please note the standard deviations  
4 which are in the final column here which are the more  
5 absolute measure of difference in performance. The  
6 lowest mean concentration tested was 6.3 units per mil  
7 and its standard deviation was 0.781, one of the  
8 lowest of those tested.

9 Please bear in mind that CVs are a  
10 mathematical calculation of the standard deviation  
11 divided by the mean concentration times 100.

12 This means that the lower the  
13 concentration, the smaller the denominator is in this  
14 calculation. The NCCLS guidelines for precision  
15 testing specify that three urine controls and five  
16 patient specimen pools will be used, assayed in  
17 duplicate, in each of two independent runs over a  
18 period of 20 days for an n of 80.

19 The agency recently brought to our  
20 attention and we agreed that it would be advisable to  
21 do additional NCCLS testing on some lower  
22 concentrations because our recommended cut off is 5.0  
23 below the 6.3 which had been previously tested.

24 Those NCCLS testing guidelines are  
25 underway now and we are testing mean concentration of

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1 about three and about five. However, we do have some  
2 data from the familiarization training for the  
3 laboratories that did site-to-site testing. This  
4 protocol is different from the NCCLS guideline. It  
5 was pre-agreed with the agency for training our  
6 laboratories. It used three urine controls and three  
7 patient specimen pools. Sorry. Specimens were  
8 assayed in replicates of four but over four days.

9 So we have a very much smaller n of 16,  
10 comparing to the n of 80 over 20 days. Looking at  
11 that data to get an indication of what the precision  
12 would be like and again this is not the same as NCCLS  
13 testing.

14 But looking at the lowest mean  
15 concentration which was tested, 3.26, here toward the  
16 middle, we came up with a standard deviation of 0.84.

17 And I've drawn the comparison for you here below.  
18 The NCCLS data, the lowest concentration tested was  
19 6.3. The standard deviation there was 0.781. So we  
20 have a very similar standard deviation. The  
21 calculation for CV divided that standard deviation by  
22 the mean concentration because the mean concentration  
23 here was half that, roughly, 3.26, the CV looks  
24 higher.

25 After the sites were trained with the

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1 familiarization protocol, one laboratory did,  
2 Laboratory One, did 100 percent of the sample testing  
3 and it was the values from that laboratory that were  
4 used for all of our calculations of effectiveness.  
5 Two other laboratories did the same subset of 263  
6 samples. And we then, using the Wilcoxon matched  
7 pairs signed rank test, recommended by Dr. Ponnappalli,  
8 compared the laboratories.

9 If you look in the final column, you can  
10 see there was a statistically significant difference  
11 between the laboratories. However, the mean and  
12 medium differences are both small and very similar,  
13 particularly between Laboratory One and Laboratory  
14 Two, there is a good deal of similarity. We then went  
15 on to investigate this range of differences to see  
16 what clinical impact it might have had.

17 I apologize that this is a bit busy, but  
18 the alternative was to have you look at three slides  
19 flipped over and use your mental memory to remember  
20 how it sits. If you look down around the proposed cut  
21 off of five and the previous cut off for monitoring of  
22 ten, you can see that in these regression analyses,  
23 the data clusters very closely together. Where we  
24 have the wider variation, the 15, ten, etcetera, is  
25 well over 40, well above the recommended cut off.

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1           Such that a change of ten or 15 units,  
2 well ont preferable, does not affect where a patient's  
3 value would fall in positive or negative range.  
4 Finally, we looked at concordance and discordance  
5 between laboratories. Concordance was to find as the  
6 NMP22 value being either above or below the cut off  
7 value at both laboratories. Here you can see that at  
8 a cut off of ten, across all three laboratories, the  
9 concordance was very similar and at the cut off of  
10 five, across all three laboratories, I'm looking in  
11 this column here, was similar.

12           The concordance was somewhat higher at the  
13 cut off of ten. To look at why that might be, we went  
14 back to our original data from the PMA, here for you  
15 below, actually if you would push the slide up a  
16 little bit, thank you -- which used a larger number.  
17 Site-to-site in this study used only two laboratories  
18 but both laboratories did 100 percent of the samples  
19 which was over 1,000 samples.

20           If we look at the cut offs of five and ten  
21 in that data, you can see that while again the  
22 concordance is a little higher at the cut off of then,  
23 the concordance is very good at the cut off of five.  
24 And I think we have had an issue here that the more  
25 samples you do, the better your concordance, bearing

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1 in mind that NMP22 is generally analyzed at large  
2 reference laboratories that are doing thousands of  
3 samples.

4 In summary, for the non-clinical data, the  
5 NCCLS precision testing data was within acceptable  
6 ranges of CVs and the lowest concentration tested, 6.3  
7 units per mil, had a standard deviation of 0.781.  
8 Additional testing of lower concentrations is  
9 underway. Familiarization data, done under a  
10 different protocol with a smaller n, showed that at  
11 the lowest concentration tested there, roughly half  
12 that and a value similar to the median concentrations  
13 for the non-cancer population in this study, had a  
14 standard deviation of 0.84, similar to that for 6.3.

15 Site-to-site comparison showed small mean  
16 and median differences and reproducibility which had  
17 been demonstrated previously in the PMA, also showed  
18 good concordance values. In developing our clinical  
19 protocol we had the advantage of the input and  
20 expertise of the agency as well as a number of  
21 Urologists across the country. In choosing our  
22 clinical sites, some of our investigators had  
23 experience with NMP22, but we were more concerned with  
24 getting a good geographical spread, as well as a  
25 variety of incidence rates.

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1           And we chose investigators from types of  
2 practices ranging from private practice to Veterans'  
3 hospitals, community hospitals and teaching academic  
4 centers. I'd like to turn over the clinical  
5 discussion now to one of our investigators, Dr. Bruce  
6 Malkowicz, the co-Director of the Urology/Oncology  
7 Program at the University of Pennsylvania Health  
8 Systems.

9           DR. MALKOWICZ: Thank you and good  
10 morning. And for giving me this opportunity to  
11 discuss the clinical trial portion of this study with  
12 you.

13           This is a protocol design for this  
14 investigation of NMP22. It's a prospective design,  
15 looking at this nuclear matrix protein as an aid in  
16 the differential diagnosis of patients with unresolved  
17 hematuria or other risk factors. So it was different  
18 than the other studies that had been performed with  
19 this agent because it was prospective in its nature  
20 and it was looking at a different patient population.

21           The enrollment occurred roughly over one  
22 year, from April through May, '98, through '99,  
23 utilizing about 33 sites. The majority of people were  
24 not currently using this in their monitoring practice  
25 and all eligible patients were asked to participate in

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1 the study. The principle objective of the study was  
2 to determine the utility of NMP22 levels in the  
3 differential diagnosis of patients with unresolved  
4 hematuria or other indications at risk for  
5 transitional cell carcinoma.

6 Secondary endpoints were to define the  
7 sensitivity and specificity of this assay to detect  
8 newly diagnosed transitional cell carcinoma in this  
9 population and stratify it by stage and grade and also  
10 to define the range of NMP22 levels in the urine of  
11 patients with newly diagnosed transitional cell  
12 carcinoma and stratify this by stage and grade.

13 Furthermore, to define the range of NMP22 levels in  
14 the urine of patients with benign disease of the  
15 urinary tract.

16 The patients at risk were those with  
17 unresolved hematuria and/or other risk factors for  
18 transitional cell carcinoma, including dysuria,  
19 exposure to carcinogens or a long history of smoking.

20 Patients must have been about to undergo a urologic  
21 evaluation which included voided cytology, cystoscopy  
22 and upper tract imaging. Patients must not have had a  
23 history of cancer of any other type except non-  
24 melanomatus skin cancer.

25 There are some other patients selected,

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1 other, besides the risk populations. These included  
2 patients with malignancies, other than urinary tract  
3 carcinoma. This was done at some selected sites.  
4 There were also exclusion criteria in that they were  
5 not undergoing any chemotherapy or biologic response  
6 therapy or radiation therapy, at the time of their  
7 urine collection. Some sites collected only normal,  
8 health volunteers, age 50 or greater with no  
9 significant medical conditions and dipstick negative  
10 urine.

11 Exclusion criteria were those patients who  
12 had been diagnosed with a urinary tract condition  
13 within the prior 12 months. They may have not had any  
14 previous history of cancer in the risk group. These  
15 are the demographics of the baseline for  
16 characteristics. Since this is somewhat of a busy  
17 slide, but if you really look at the sets distribution  
18 go along the lines here. You have a fairly even  
19 distribution, about 53/47 for male to female. Also a  
20 good representation of African-American patients  
21 within this group.

22 And the distribution essentially showed  
23 that when you go through all this, that the cancers  
24 tended to be concentrated in older, white, male  
25 patients with a heavy smoking history, which is not

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1 unsuspected. The NMP22 values were studied mainly for  
2 their median because of the kind of skewed  
3 distribution that you see. And I'll just sort of give  
4 a better representation of the values, the medians  
5 were used.

6 And here you can see that normal, no  
7 disease of the urinary tract, those are benign  
8 conditions. All had values well under five and those  
9 with urinary tract carcinoma had high values,  
10 essentially 12.6 is the median. And these expected  
11 values, when you looked at the diagnostic study and  
12 patients without cancer, the area to really  
13 concentrate on is the second column, zero to less than  
14 five, where the predominant majority of patients  
15 presented, and this is all on males. Females, those  
16 with a benign disease, those with other cancers. And  
17 then this quickly fades out as these values start to  
18 rise.

19 The distribution of NMP22 values in the  
20 risk patients were highly concentrated in those  
21 patients who had transitional cell carcinoma in the  
22 upper ranges. And those patients with no urinary  
23 tract disease, the concentration, again, was in that  
24 zero to five range. This is scattergram and it's  
25 showing again the quintiles here 90th through the

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1 70th, and 25th distributions. And the groupings  
2 showing that there was no bimodal distribution, that  
3 there tends to skew off to some degree, either those  
4 with cancer, no disease, benign condition, health  
5 patients and some with other carcinomas.

6 Again, high concentrations at very low  
7 levels for those with no or benign disease or those  
8 populations which were healthy. And a wider  
9 distribution of values in those with transitional cell  
10 carcinoma of the bladder. The next issue with this  
11 data was to decide on cut offs. A previous indication  
12 for this agent has been used as an aid in management.

13 and there you are using a different population,  
14 you're monitoring for recurrent disease and cut off  
15 values of ten have been chosen.

16 There are some smaller independent studies  
17 looked at by physicians and other institutions that  
18 use the cut off between six and ten. This gave some  
19 baseline and getting a feeler, one might go with this  
20 different population and that was used as an aid to  
21 more standard traditions, statistical traditions in  
22 utilizing ROC analysis and evaluating different  
23 multiple cut offs, looking for acceptability between  
24 sensitivity and specificity.

25 And the perspective here was, since this

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1 was being used as an additional test with imaging,  
2 physical visualization of the urethelium, and  
3 cytology, look for an optimization, a sensitivity.  
4 Also this is an aid in diagnosis, so you're looking at  
5 a different group and the optimal cut off point here  
6 came at five units per milliliter. And there's ROC  
7 curves that would show that also.

8           These are the trials that we were talking  
9 about before. You're looking at levels that came out  
10 essentially at about six, one study lower in this  
11 area, used ten as a cut off, this was somewhat  
12 different as the single institution study. This  
13 grouping and population had about 50 percent of their  
14 patients with much higher grade and higher stage  
15 carcinoma. It should be mentioned that generally  
16 about 80 percent of the patients who would have  
17 carcinoma, would be superficial disease.

18           About 20 percent, 25 percent muscle  
19 invasive disease. And that was essentially the  
20 distribution you saw in this multi-institutional  
21 study. That's one particular study that had almost up  
22 to 50 percent of patients with muscle invasive  
23 disease, hence the difference that they chose in their  
24 cut offs in doing their sensitivity analysis. And  
25 again, here's the ROC curve where we looked at the

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1 optimal finding here, the area on the curve being  
2 about 73.

3 And when you looked at this, just a visual  
4 inspection and also statistical analysis suggests that  
5 five is a reasonable cut off for optimization in this  
6 particular study with this cohort. And here again,  
7 when it looks at the sensitivity and specificity,  
8 cutting off at different values. And again, the key  
9 issue here is five, whatever was chose for this study,  
10 some numerical increments going one way or another.  
11 Here you're picking up a little bit on specificity and  
12 incremental increases starting, not getting any gain  
13 in your sensitivity and then a very significant drop  
14 off in sensitivity if you use older values in this  
15 case.

16 So essentially, optimization, just  
17 numerically an inspection of this occurred at 5.0 with  
18 this particular cohort. And the diagnosis, a  
19 transitional cell carcinoma of the bladder, using this  
20 cut off, you can see that NMP22 at this cut off for  
21 sensitivity is more than twice as sensitive as voided  
22 cytology providing you the information which one would  
23 want to extract at this point. Specificity was  
24 acceptable, again voided cytology being a goal  
25 standard for specificity at 100 percent.

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1           When one combined these values, you found  
2 that, again, superiority over voided cytology without  
3 any loss, without significant loss in specificity. In  
4 looking at this as a breakdown in stage-by-stage, we  
5 see that NMP22 at this cut off provides a greater  
6 percentage of findings than voided cytology at every  
7 level. Again, these numbers are most significant in  
8 the pre-malignant condition in the lower grade tumors,  
9 providing much better pick up at these levels than  
10 cytology alone.

11           And again, combined values being quite  
12 useful, it's important also to note that for carcinoma  
13 in situ and muscle invasive disease, combinations of a  
14 NMP22 and cytology found every person within those  
15 cohorts for 100 percent pick up. And you look at this  
16 by grade, again, an advantage found in low grade or  
17 pre-malignant conditions, that was very striking and  
18 very robust and still significant of numerical  
19 significance at the medium and high grade levels.

20           In summary, NMP22 is a non-invasive test,  
21 it carries not risk to the patient, any morbidity. It  
22 requires a single voided urine sample. There is no  
23 interference from hematuria, as shown from prior  
24 studies. It's twice as sensitive as voided cytology.

25           It's for a bladder carcinoma. And more than twice

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1 as sensitive in finding early and non-invasive cancers  
2 and pre-cancerous legions, detecting 63 versus about  
3 28 percent identified by cytology.

4 NMP22 identified 84.6 percent of invasive  
5 tumors when voided cytology detected only 55 percent.

6 And together they identified 100 percent of the  
7 carcinoma in situ and muscle invasive legions. NMP2  
8 detected the majority of the pre-cancerous papillomas  
9 and voided cytology detected none. And NMP22 is not  
10 dependent on visual or morphologic changes. Different  
11 cut off values were recommended as opposed to prior  
12 studies because this is an indication for diagnosis,  
13 aid in diagnosis as opposed to monitoring. And  
14 therefore optimal sensitivity was the key for this  
15 different patient population.

16 In conclusion, this assay improves the  
17 potential for the detection of early, more easily  
18 treatable tumors without increasing any risk to the  
19 patient. Prognosis for patients who's cancers are  
20 diagnosed at an early stage are generally better and  
21 expenses are reduced in terms of their need for less  
22 aggressive therapy and fewer surgeries for recurrent  
23 and progressive tumors. NMP22 is safe, effective,  
24 it's a low cost adjunctive test which can aid in the  
25 diagnosis of urinary tract tumors and has the

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1 potential to enhance the sensitivity of our present  
2 evaluation. Thank you.

3 CHAIRMAN LADOULIS: Thank you, Dr.  
4 Malkowicz.

5 Are there any questions from Members of  
6 the Panel about this presentation?

7 DR. CARPENTER: Yes, I have a question  
8 about a CIS. As we all know, that is an area where,  
9 of great concern because it's in contrast to papillary  
10 TCC, it's a precursor, often a precursor invasive  
11 disease. So one thing I wondered, you only had five  
12 patients that you looked at, CIS. I wondered if you'd  
13 done any other studies with more patients that had  
14 presented with CIS?

15 DR. MALKOWICZ: Specifically, no. That's  
16 what actually came up in that group. And when you  
17 look at a lot of the marker tests too, we always  
18 consider this a very important cohort, but it's not  
19 always a very enriched population when you look at all  
20 of these studies. Even other markers that  
21 investigated this area always make strong points about  
22 carcinoma in situ, but when you look at the raw  
23 numbers, they are not particularly robust.

24 But I think going across a multi-  
25 institutional study, across the country, this is what

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1 we see. It's a very lethal, it's a very dangerous,  
2 it's a very concerning disease, but it's not quite up  
3 at the level of major carcinoma that we see regularly.

4 So this is about the best we can see in these numbers  
5 right now.

6 CHAIRMAN LADOULIS: Yes, Dr. Taube.

7 DR. TAUBE: In the clinical study that you  
8 ran, you selected patients who were at risk based on  
9 the factors that we heard. And all of these patients  
10 must have been about to undergo neurologic  
11 examination. How do you anticipate using this test in  
12 the general population, not in a clinical study? I  
13 mean on what patients would you use the test?

14 DR. MALKOWICZ: Yeah. When you look at  
15 the evaluation for hematuria, across the country, it's  
16 very varied. At some institutions somebody walks into  
17 the door and they have trace hematuria, it triggers a  
18 full examination, just 100 percent sensitivity issue.

19 With other people there is a little bit more  
20 discernment, a little bit more bargaining and weighing  
21 these issues with patients.

22 And I think what this would do or maybe a  
23 person seems a little bit younger, out of a cohort,  
24 maybe this person, you know we don't want to be  
25 invasive, the patient is a little bit reluctant. You

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1 say, this is something you can add into the dialogue  
2 saying, maybe these numbers are abnormal and this may  
3 weigh into your decision whether or not you want to go  
4 for an evaluation. Or should we come back again and  
5 look at this. Or physicians who haven't been  
6 dismissing some hematuria might say, hmm, this may add  
7 in a little bit more in terms of what we need to do  
8 with it.

9 Or when I'm doing the cystoscopy, some  
10 people may do flexible cystoscopy and that tends to  
11 have slightly less resolution than a rigid cystoscopic  
12 examination which in men is more uncomfortable. You  
13 might say, well, in this case, things are adding up  
14 where there may be a greater sense for positivity,  
15 let's go and do the entire full exam as clear as  
16 possible because there is an indication here that  
17 there might be more trouble than we suspect. And it  
18 would cause you to be a little bit more thorough.

19 DR. TAUBE: Given that, can I pursue this  
20 a little bit.

21 CHAIRMAN LADOULIS: Proceed.

22 DR. TAUBE: I was thinking about this and  
23 came up with a series of scenarios. Because there are  
24 implications, based on what you just said. I mean  
25 supposing a woman of 40 years of age with no smoking

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1 history, came into a doctor's office with some other  
2 indication and had a urinalysis and there was micro  
3 hematuria. Without this test, what's the likely  
4 scenario for the work up of this patient?

5 DR. MALKOWICZ: Again, it depends on the  
6 institution. Unfortunately, we're in the middle of  
7 this. In Urology you need to have an AUA Guidelines  
8 Panel hasn't reported its results yet, but Ed  
9 Messingness is actually running this. At our  
10 institution that person is getting evaluated because  
11 we tend to be the tertiary center that sees the people  
12 who are dismissed for several years and all of a  
13 sudden they walk in and they have a tumor in their  
14 bladder or some other condition related to that.  
15 Another situation that's not unreasonable, and there's  
16 no set standard that that person should be ignored or  
17 be counseled or looked at in that situation.

18 I think a person, and again it's been my  
19 practice to always be in a dialogue with a person and  
20 not be, you know, absolutist in this but think, well,  
21 you've had this hematuria, your family doctor has  
22 found it on two occasions, it's probably nothing but  
23 now you've got this other test that's not 100 percent,  
24 but it suggests there might be something there. So if  
25 you want to open up this door, it probably is worth

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1 looking at and you're removing this small chance.

2 What do you feel comfortable with? Do you  
3 feel with the small chance that you might have cancer  
4 and want to leave this alone, relative to the studies?

5 Or do you want to know what's going on? And one  
6 patient will say, I've had three family members who  
7 have had carcinoma, I want to make sure I don't have  
8 cancer. The other person will say, look, I've got a  
9 million appointments and I'm late for this and I've  
10 got other things to do and I still feel pretty  
11 comfortable with this and this isn't 100 percent,  
12 let's just check it again in three months and I'll go  
13 along.

14 So you have to use it. You're not going  
15 to use it as yes or no. I think if you use that as an  
16 absolutist point, it's not particularly good medicine.

17 But it's just another weighing in factor that someone  
18 should use.

19 DR. TAUBE: Because based on the data and  
20 the use of a five unit --

21 DR. MALKOWICZ: Right.

22 DR. TAUBE: -- cut off, approximately 25  
23 percent of women under the age of 50 might have a  
24 positive test.

25 DR. MALKOWICZ: Right.

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1 DR. TAUBE: And so that would mean that  
2 you would be saying to many women, who's risk for --

3 DR. MALKOWICZ: Carcinoma --

4 DR. TAUBE: -- carcinoma of the bladder is  
5 very small and certainly at the age of 40. So the  
6 question is really would this trigger additional, more  
7 invasive tests than the women might otherwise undergo  
8 without this test in the picture.

9 DR. MALKOWICZ: I think it should trigger  
10 more discussion, but not necessarily a reflex to  
11 testing. I mean that's the way we've approached it.

12 CHAIRMAN LADOULIS: Any other questions?

13 Dr. Hortin.

14 DR. HORTIN: I have a couple of questions.  
15 First of all, in the cancer study population for the  
16 transitional cell cancers, were these all bladder  
17 cancers or were some of them like renal pelvis, ureter  
18 or, what was the population of cancers?

19 DR. DOMURAD: This clinical trial, now  
20 that we are discussing? They were bladder cancers.  
21 We were open, we were prepared to find ureteral  
22 cancers or others and the evaluation is essentially  
23 the same, but the cancers that were found, were  
24 bladder cancers.

25 DR. HORTIN: Now the issue that troubled

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1 me a little bit was that for every urinary  
2 quantitative marker that I could think of, basically  
3 there is some adjustment for urine concentration, say  
4 creatinine or osmolality or others. If you take  
5 markers, say like urine albumin output, even sodium  
6 potassium. We're either doing a timed measurement to  
7 do a measurement over a period of time or some  
8 adjustment for urine concentration.

9 I didn't see where you had any collection  
10 criteria in terms of rejection of say those specific  
11 gravity samples or any effort to adjust your  
12 quantitative measurements for an estimate of urine  
13 concentration. What is your rationale for why you  
14 should not have, why your results would not be  
15 improved by entering in some measure of either urinary  
16 output, timed output or creatinine measurement.

17 It would seem that if somebody is having  
18 an output of, a very high output of five liters per  
19 day versus somebody is having a 500 mil output per  
20 day, that the concentration would change by a factor  
21 of ten based simply on their fluid intake.

22 DR. DOMURAD: It's a very good question  
23 and the reason you did not see the information in this  
24 submission is a number of things were included in this  
25 submission by reference to the original PMA. And

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1 those tests were all done with the original PMA.  
2 Specific gravity, concentration, creatinine, etcetera.

3 And there was found to be no significant difference  
4 from variation. So those tests were done, Dr. Hortin.

5 They weren't done for this study because they had  
6 already been shown.

7 CHAIRMAN LADOULIS: Yes. Dr. Petrylak.

8 DR. PETRYLAK: Yes, was, since you're  
9 taking patients who are higher risk, I assume that the  
10 histologies that you picked up, at least by your  
11 presentation, were all transitional cell or did you  
12 pick up any atypical histologies, such as squamous or  
13 small cell or adeno, which is some studies can make up  
14 as high as ten percent of your population?

15 DR. MALKOWICZ: No, this was actually,  
16 when we looked through the data it all ended up being  
17 TCC and it didn't get a distribution of some of the  
18 rarer cancers that we see.

19 DR. PETRYLAK: Do you have any data  
20 looking at this with some of the rarer cancers?

21 DR. DOMURAD: In the original PMA there  
22 were three cancers, total, that turned out to be  
23 squamous cell. And it was determined by the agency,  
24 upon review, that that was not a large enough number  
25 to make any conclusion.

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1 CHAIRMAN LADOULIS: Yes, Dr. Berry.

2 DR. BERRY: Dr. Malkowicz, you indicated  
3 that five seemed to me optimal or appealing in some  
4 fashion and I didn't see that. I mean you, this is a  
5 balance of false negatives and false positives and  
6 decreasing to five, increases the false positive rates  
7 and I'm sure, I'm concerned about that and this has to  
8 do with Dr. Taube's question. You know, the  
9 subsequent management --

10 DR. MALKOWICZ: Right.

11 DR. BERRY: -- and the, first why is, why  
12 is five appropriate and why is it an appropriate  
13 balance?

14 DR. MALKOWICZ: Because if this were, the  
15 difference I think is between using it as an isolated  
16 test versus using it in conjunction with a lot of the  
17 other issues. A lot of, you know, like voided  
18 cytology. And with the voided cytology, the one  
19 quality that that has is its specificity. So we  
20 weren't, the issue wasn't so much towards the  
21 specificity, as trying to optimize sensitivity in this  
22 case and getting that placed in an appropriate  
23 context.

24 And when you, the one slide I had going  
25 from four up to ten, seemed that the balance of

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1 numbers and that sort of comes out to the area under  
2 the curve, if you're familiar with that, it came in at  
3 that point where you had about 70 and 68 percent. And  
4 then you sort of dropped off in your sensitivity.  
5 When we used the older numbers of ten that you used  
6 for monitoring, it was like 52 percent and then the  
7 specificity was up to 86.

8 But if you're using cytology, already  
9 you're getting good specificity so the loss in  
10 sensitivity kind of negates what the particular value  
11 for this is. So that seemed to be the balance point  
12 at least in my opinion and that of some of the other  
13 Urologists involved in this for trying to detect  
14 disease. This issue to, that comes up, you know, with  
15 Urology and looking at transitional cell carcinomas,  
16 our goal standard is a shaky one.

17 In that cystoscopy, negative cystoscopy  
18 doesn't mean the privation of disease. That's a  
19 problem that we're stuck with. And that accounts for  
20 some of the skew that we see in a few of these other  
21 things. And a lot of these people, and there's a  
22 follow up study going on and some other people looking  
23 at markers have looked at this issue in different  
24 kinds of statistical analysis, like hazard analysis.

25 So the idea here was not to miss too much.

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1 If you sort of played around with some of the values,  
2 say four or six or seven, you really didn't change  
3 those numbers too much. They really started changing  
4 numerically as you hit ten. So again, just saying the  
5 idea was to optimize sensitivity here since you're  
6 already using a highly specific test in conjunction.  
7 And this isn't being used just, you know, alone, in  
8 vacuo, so that's why that was chosen.

9 DR. BERRY: This is, you addressed some of  
10 this in responding to Dr. Taube, but with false  
11 positives, what happens when a patient gets a large  
12 value and is told, your marker is high, what is the  
13 subsequent management?

14 DR. MALKOWICZ: Well, I think I had  
15 someone say they were going to repeat this again and  
16 see whether it's gone down. And again, it depends on  
17 the particular patient. If this is someone who has  
18 had hematuria, has been seen two or three times by  
19 their family doctor. They're coming to see you,  
20 probably saying, you know, he said come and see you, I  
21 want to see you, let's just see what it's about.

22 And that's the only issue that came up, I  
23 think after you've come to that, that one value as  
24 being the only negative, you say, well, it's here. I  
25 think if you're responsible, a reasonable dialogue is

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1 to say, we probably won't find anything, but this is a  
2 yellow light, let's look both ways before we cross the  
3 street and take care of it at this point, because  
4 we've been following you for a year or two or your  
5 family doctor has been following you for a year or  
6 two.

7 You know, it's time to try to either bring  
8 some closure to this and clear it out. And most  
9 likely you are going to be fine and you can move on  
10 with your life. For someone who it's the first  
11 initial finding, yeah, you had some blood in your  
12 urine and maybe their family doctor had been burned a  
13 week or two before by somebody else who had been out  
14 and they had followed for a long time and then ended  
15 up having bladder cancer. You might say, well, it's  
16 the first finding, it's there, this is not a yes or no  
17 test, it's not an oracle. It kind of weights things a  
18 little bit towards that it might be worth evaluating.

19 And if they say, well, I don't want to do  
20 it right now, I think that everything else looks okay,  
21 it was only a trace, it wasn't much blood. I said,  
22 well, let's check it out in another three months or so  
23 and let's not lose sight of that. I mean, that would  
24 be a responsible way of doing it. But just to say,  
25 oh, this is, it crossed the threshold, you need this

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1 entire workup or this is not, isn't a responsible way  
2 to go with it. That's how we would handle it.

3 DR. BERRY: But does it increase the  
4 patient's psychological stress? Have there been  
5 studies looking at that? Or do you have any feeling  
6 about that?

7 DR. MALKOWICZ: The only way I could  
8 correlate stress in terms of marker issues is my day-  
9 to-day involvement with dealing with PSA values and  
10 dealing with men and prostate cancer. And that's a  
11 definite reality where people do become concerned  
12 about those issues. But I think it's, again,  
13 something where if you dismiss it as, oh, it's up, you  
14 need a biopsy, oh, it's down, you don't need this.  
15 It's how that interaction occurs between the physician  
16 and the patient who needs something, that could create  
17 a very stressful situation if it's just dismissed and  
18 say it's abnormal, it's your problem, you have to deal  
19 with it.

20 Or if you say, there's ups and there's  
21 downs, this is a yellow flag, let's just look at it  
22 again. Let's just decide, where do you feel  
23 comfortable, where is your level of comfort in this?  
24 And true, and say up front, more than likely this will  
25 be negative, in more cases than not, most evaluations

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1 for bladder cancer are negative. But when we do find  
2 something, we find something significant. If we miss  
3 something that's significant, it becomes very, very  
4 significant.

5 So, it depends on how you, as the  
6 physician, lay it out for the patient. Just say,  
7 there's something here, but it needs some follow up.  
8 We're not going to lose sleep over it or toss and  
9 turn, but don't dismiss it and don't just walk away  
10 from it and get on with your busy life. Just revisit  
11 it again. It's a lot of words, but this is what we do  
12 in the office these days, is a lot of talking back and  
13 forth with the patients.

14 CHAIRMAN LADOULIS: Dr. DiLoreto.

15 DR. DILORETO: I think that getting, or  
16 going back to what Dr. Taube was talking about, we  
17 have to put things into perspective. The work up for  
18 hematuria or micro-hematuria isn't just for  
19 transitional cell lesions, it's for GU pathology. And  
20 fortunately the TCCs are not what we find all the  
21 time, but there is significant pathology that we're  
22 looking for.

23 And this test or any other test like this  
24 is only an aid in the diagnosis of a particular  
25 lesion. The standard of care, and it may evolve to be

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1 something different, given some time down the road  
2 with some clinical experience with tests like these or  
3 others, the standard of care is upper tract and lower  
4 tract evaluation. And that's what's taught to all  
5 residents in all places. They require some kind of  
6 upper tract evaluation and some kind of lower tract  
7 evaluation.

8 It's sort of the soup du jour of what  
9 combo you would like to do, but those two things are  
10 done. I think what is significant is, as was  
11 mentioned earlier, was optimizing the sensitivity of  
12 this test. You're looking for tumors in high risk  
13 population. The current standard is doing flexible  
14 cystos in the office. That is significantly less  
15 desirable, from a diagnostic standpoint, than previous  
16 experience doing rigid cystos. And there in fact is,  
17 and it was referenced in the article here, the  
18 studies, European studies where there's only a 47  
19 percent sensitivity of using rigid cystos to diagnose  
20 bladder cancer.

21 I would believe to be even less than that  
22 doing office space flexible cystos. If you can  
23 combine certain tests to increase the sensitivity of  
24 picking up these lesions, i.e., cysto upper tract  
25 studies, obviously for other pathology, and cytology

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1 as well as a test like this and come up with close to  
2 100 percent sensitivity, you're doing very well. And  
3 the significance of that, I think, is going to be very  
4 positive in the clinical environment.

5 How the product is labeled, when it goes  
6 out, when whatever we recommend, and what, and how  
7 it's used, maybe two different things. But I think  
8 the labeling has to be very stringent in that this is  
9 an aid in the diagnosis and that it should not be  
10 allowed to be out as a screening test to be done by  
11 the PCPs, etcetera, etcetera, of the world. That  
12 somebody shows up with micro-hematuria, they do this  
13 test and then they're done. Because they are going to  
14 miss tumors, they are going to miss other GU pathology  
15 that's significant, that could be significantly, a  
16 significant clinical issue for that patient.

17 So again, a lot of it depends on where we  
18 are and what we recommend from a standpoint of  
19 labeling of this. Until such time, five years from  
20 now or whatever, that we could safely say, you don't  
21 need to do a cysto. You know, you do this and this  
22 and you don't have any tumors, well, that may come to  
23 pass. It may never come to pass, but again, that  
24 only, that only is the issue of tumor pick ups, not GU  
25 pathology pick ups.

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1 CHAIRMAN LADOULIS: That's good. I'd like  
2 to back up and make some comments as well. I think  
3 some of the same concerns that have been expressed  
4 here have come before this Panel and some of its  
5 people with regard to the PSA, for the obvious reasons  
6 that Dr. Malkowicz pointed out. When it was an issue  
7 as to having such a marker, the concerns are what the  
8 eventual practice would be once the device is brought  
9 to market. And it was approved, for example, as an  
10 aid to diagnosis with digital rectal exam and PSA  
11 test.

12 And in practice it has, I think, evolved  
13 largely as a, in many hands, in the wider clinical use  
14 almost as a screening test. With obvious concerns.  
15 And I think that concerns were felt even then. And I  
16 think some of the concerns I have, have to do with  
17 this cut off value and the eventual application by  
18 clinicians other than those in tertiary care medical  
19 centers like yours. And in many of the other sites.  
20 They will be used in many practices and will be relied  
21 upon if it is approved in the same, at the same cut  
22 off level as now, and used in a much wider population.

23 Now in your data and in the presentation,  
24 you alluded to the fact that some of the previous  
25 studies in which the specificity and sensitivity were

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1 defined were in cases and in studies with large  
2 populations of already diagnosed cancer or already  
3 suspicious of cancer population. Whereas the  
4 incidence of this disease in the general population is  
5 maybe four, six, eight percent, seven percent,  
6 somewhere in that range.

7 DR. DOMURAD: About seven percent.

8 CHAIRMAN LADOULIS: So that the positive  
9 predicted data calculations for this, I'd like you to  
10 go into again, if you could, as you had in the  
11 presentation. And if you could go through those  
12 calculations for us because this addresses the issue  
13 that Dr. Taube, I guess, and Dr. Berry presented, is  
14 that in the general population, even if you allow for  
15 the fact that patients with hematuria might be coming  
16 to the office in many practices and even family care  
17 settings, the tendency might be to use this test and  
18 to use it in the way it's proposed, and what would be  
19 the positive predictive value and what would be the  
20 false positives that might result from this  
21 application, given the prevalence of this disease.

22 I point out that even in your submission,  
23 you know, bladder calculi is probably one of the  
24 prominent causes of an elevated NNP, as well as renal  
25 carcinoma in the one case and upper urinary tract,

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1 which raises the issue that Dr. Petrylak proposed,  
2 that it might pick up inadvertent or unsuspected renal  
3 cell carcinoma, but urinary calculi are much more  
4 common and probably might be responsible for a large  
5 number of cases with elevated NMP22.

6 So the question is, what is the false  
7 positive rate expected to be with this cut off of five  
8 and, or the alternative and what is the positive  
9 predictive value and is it acceptable clinically and  
10 to the clinicians around the table?

11 DR. MALKOWICZ: Well, the positive  
12 predictive value at the calculated level is about 15  
13 percent or so. So it is lower. And that was again  
14 because of the population that you're looking at and  
15 the amount of the disease incidence that you see in a  
16 large population. So that's the trade off issue that  
17 it goes with the sensitivity that you're dealing with  
18 in this case. And again, if some were to just apply  
19 it blindly as a "screening" test, which is not the  
20 intent here at all, but more of a, something that's  
21 going to be used, I see it more from the urologic  
22 perspective when somebody is getting everything in  
23 order to finally evaluate a patient as it's use.

24 As you start stretching, if you want to  
25 start stretching limitations beyond what anyone in the

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1 study, or what I would write up in the paper would be,  
2 then I think there would be a potential to be over  
3 extending the issue and getting a fair amount of false  
4 positivity in these patients. Now false positive,  
5 again, in the appropriate patients, it's not so much  
6 that someone is a very low risk patient, it's  
7 different than false positive in a higher risk  
8 patient.

9 A pack-a-day smoker and a man over 50 who  
10 has a false positive, that still needs to be defined  
11 because a negative cystoscopy doesn't mean that it is  
12 false positive. In a younger woman, again, that's an  
13 issue, I think, where you'd have to sort those issues  
14 out more carefully. And the potential, if you had an  
15 over broad application of this, is bothersome, but  
16 again, by the nature of how the indication is used.

17 Again, I'm not part of that. I'm mainly  
18 clinical investigator and saying exactly how they're  
19 going to write everything up. But the part of the  
20 indication, I think, is part of the urologic  
21 evaluation, not as a screening by a family physician  
22 in using that. So that's where the interest is sort  
23 of concentrated in.

24 DR. DOMURAD: If I may amplify that, as  
25 well.

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1 CHAIRMAN LADOULIS: Yes, please.

2 DR. DOMURAD: And I see Dr. DiLoreto's  
3 hand up and I'm going to follow on to one of this  
4 comments.

5 DR. DOMURAD: The positive predictive  
6 value is dealing specifically with tumors found and  
7 there is a some concentration here that if a patient  
8 doesn't have a tumor, then they didn't need a  
9 cystoscopy or another evaluation, which isn't true.  
10 If a patient had urological disease, they need that  
11 evaluation. And yes there are some higher NMP22  
12 values with calculi, but that doesn't mean that that  
13 patient should not have undergone upper tract  
14 evaluation and cystoscopy. Stones need to be treated.  
15 Cystitis needs to be evaluated and treated.

16 So because a patient does not have a  
17 tumor, does not mean that they are getting an  
18 unnecessary evaluation.

19 CHAIRMAN LADOULIS: No, but would the  
20 value return on an abnormally high on NMP22, raise a  
21 suspicion in the clinician's mind and relay that to  
22 the patient that they may have a tumor or they have in  
23 fact calculi?

24 DR. TAUBE: I mean the indicated use, the  
25 intended use is as an aid in the diagnosis of persons

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1 with symptoms or risk factors for transitional cell  
2 cancer of the bladder. So the intended use is to pick  
3 up cancers, not calculi.

4 DR. DOMURAD: Yes, it is, I agree, it is  
5 to identify, as an aid in identifying cancer. I just  
6 wanted to draw a difference that if it doesn't find  
7 the cancer, it doesn't mean that it necessarily caused  
8 an unnecessary evaluation.

9 DR. DILORETO: Can I comment?

10 CHAIRMAN LADOULIS: Dr. DiLoreto.

11 DR. DILORETO: Because there is an analogy  
12 that's clinically very common today. And that's doing  
13 a cytology evaluation in this same patient population,  
14 but if the cytology comes back atypical, which is a  
15 very common finding, and it's no different in my mind  
16 that what would come up in this particular case. What  
17 that would entail is that it would be a higher index  
18 of suspicion of the clinician to pay closer attention  
19 to what's going on, not labeling them psychologically  
20 or whatever that they have a cancer, but it is the  
21 onus of the clinician to either follow them more  
22 closely or do something, you know, do something more.

23 The analogy would be a CIS situation,  
24 which given the presentation, and I agree is a very  
25 small population, those are the ones we get into

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1 trouble with. And you may do a cysto. You may do a  
2 cytology. You may do an NMP22 and come up with this  
3 equivocal group of patients. You're going to back in  
4 and redo a cysto and probably do random biopsies on  
5 those patients that you wouldn't do in a population  
6 that didn't have a false positive, or didn't have an  
7 atypical or positive cytology and look closer.

8 So again, I think the issue is an aid in  
9 diagnosis. It doesn't preclude that they are not  
10 going to get evaluated and it doesn't mean that they  
11 are going to be left alone and nothing more is going  
12 to happen with them. It's, I mean these are clinical  
13 judgements that are going to have to be made down the  
14 road, given the facts put in front of a clinician.  
15 And I think this is a plus, putting those things in  
16 perspective, to look harder if there's a reason to  
17 look harder.

18 And currently we don't have reasons to  
19 look harder, other than atypical cytologies, which are  
20 ubiquitous, to say the least.

21 CHAIRMAN LADOULIS: Yes, Dr. Kemeny.

22 DR. KEMENY: I agree with this and also  
23 the other thing is that, I mean again, we have to look  
24 at this as an aid in diagnosing the cancer and it's  
25 interesting, I thought it was interesting to see how,

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1 I mean the level that you'd want five as a cut off and  
2 I agree with that. It also is interesting to see how  
3 this might correlate in the future, the testing hasn't  
4 been done, with perhaps, with grade or severity of the  
5 cancer and that's already kind of an interesting thing  
6 about this marker.

7 That with the transitional cell cancers,  
8 you saw that the majority that were higher than even  
9 this level. So, I mean I think this looks like a good  
10 aid for diagnosis.

11 CHAIRMAN LADOULIS: Dr. Berry.

12 DR. BERRY: I have a comment or a question  
13 about the conclusion that you made, Dr. Malkowicz.  
14 It's carefully worded. It says NMP22 assay improves  
15 the potential for detection of earlier and more easily  
16 treatable tumors without increasing risk to the  
17 patient. Of course there is, there are a number of  
18 biases, most notably, lead time bias in this  
19 assessment. Have there been studies that have  
20 addressed this issue and, I mean, is it really  
21 important to detect this cancer early?

22 DR. MALKOWICZ: It's important to detect  
23 the higher grade and intermediate stage tumors early.

24 When you have T-1 lesions, these are lesions that are  
25 just going into the lamina propria and maybe not quite

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1 muscle invasive or T-2 lesions which are very  
2 treatable within the muscle of the bladder and haven't  
3 gone extra-vesicle are important, because when you  
4 have high grade lesions that have a tendency to become  
5 muscle invasive and those are picked up earlier and  
6 treated earlier, the chance for cure with surgical  
7 treatment is much higher.

8           You're looking at perhaps 85 percent  
9 survival as opposed to people with extensive muscle  
10 invasive disease being down in the 50 percent range.  
11 So it is important. There isn't much in the way of  
12 screening tests. Again, there is about two studies,  
13 one that was done on a high risk population in this  
14 country and one in England. And it's inferential and  
15 actually there are small numbers, but there are  
16 numbers nonetheless that show that you pick up, you  
17 see a stage shift in getting these high grade,  
18 intermediate stage lesions picked up with this type of  
19 intervention.

20           Or you get a lot more very extensive,  
21 almost incurable disease when it just becomes an  
22 incident pick up when somebody comes in, say, with  
23 gross hematuria or some other issue. So earlier pick  
24 up, again, large, massive studies, multi-institutional  
25 screening, no. But in two or three studies with

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1 numbers in the low hundreds, you do see differences in  
2 terms of what will make a difference in saving  
3 somebody's life by getting at this early.

4 DR. BERRY: A stage shift is not  
5 necessarily lifesaving, I mean --

6 DR. MALKOWICZ: It is in bladder cancer.

7 DR. BERRY: -- because of the --

8 DR. MALKOWICZ: It is in transitional  
9 cell --

10 DR. BERRY: -- because of lead time bias.

11 DR. MALKOWICZ: No, no, no. Because if  
12 you treat, there's enough data even with cystectomy  
13 data at ten years, that shows that if you're treating  
14 T-1, Grade 3 disease or T-2 disease and doing a  
15 cystectomy on that person, the five year data is  
16 actually starting to hold up at ten years. Where  
17 you're getting 77 to 80 percent five year survival.

18 If you have extra-vesicle disease, you're  
19 down in the 50 percent and down in the 40 percent  
20 range in terms of five year survival with that. So  
21 that's not a lead issue and that's real data that is  
22 matured, actual, not actuarial data.

23 CHAIRMAN LADOULIS: Any questions? In  
24 this submission, there are, there are 56 patients,  
25 right? With urinary tract --

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1 DR. DOMURAD: Yeah.

2 CHAIRMAN LADOULIS: In contrast to the  
3 distribution among the other benign disease in the  
4 normal patients, they were almost virtually 95 percent  
5 white patients and --

6 DR. MALKOWICZ: Of the cancer patients.

7 CHAIRMAN LADOULIS: The cancer patients,  
8 yeah. And in fact the three black Americans, they  
9 median values which was actually within normal limits,  
10 right? So is there any other data that you have on  
11 other populations, other than white, that this NMP22  
12 reasonably can be assume to be valuable in other than  
13 white males or white patients over 50.

14 DR. DOMURAD: I was just going to go back  
15 to the original PMA data where numbers of minority  
16 patients were larger and it was not shown to be a  
17 difference between NMP22 values across races. Also  
18 just to step back to your comment, the American Cancer  
19 Society Publication Data for 1999, in previous years,  
20 indicates that predominantly bladder cancer is a  
21 cancer of older, smoking, white males in this country.

22 Our data is consistent with theirs in  
23 where the cancer has turned up. But the PMA data had  
24 a larger number of patients. That's the specific  
25 question.

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1 DR. MALKOWICZ: Yeah, within the cohort of  
2 patients, again, those who participated, it was about  
3 15 percent African-American. So it's a good  
4 representation of people being evaluated for  
5 hematuria. But the outcomes really do just mirror  
6 what you see in the data, and I see in my own practice  
7 at the University of cystectomy series and people that  
8 we follow that for some reason African-Americans tend  
9 to have, they are less lethal and have a much lower  
10 incidence of muscle invasive and even superficial  
11 bladder cancer.

12 There have been some hypotheses about this  
13 in terms of like allelotypic differences and like  
14 different oxidative enzymes and protected by GST  
15 systems and cyp 450 systems and other things like  
16 that. But that's what we see.

17 CHAIRMAN LADOULIS: I was curious just  
18 about one other piece of data from your actual studies  
19 in that while the patient risk factors include smoking  
20 as one of the three, that in fact what you found for  
21 the median values, of those 44 patients with cancer in  
22 the urinary tract, their median values were actually  
23 lower than those for the few patients with cancer.

24 DR. DOMURAD: Smoking alone was not a  
25 contributing factor to a high NMP22 value.

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1 CHAIRMAN LADOULIS: Okay. But clinically,  
2 that's a risk factor and it's a reasonable screening  
3 factor to include such patients for having such work  
4 up that it would include NMP22? So that risk factor  
5 in the labeling will still be identified, is that  
6 right?

7 DR. MALKOWICZ: The cohort people get  
8 cancer.

9 CHAIRMAN LADOULIS: Okay, so that the  
10 labeling claim is, for this test, would still be for  
11 patients with risk factors? Is there an age-specific  
12 limitation that you would place -- you mentioned  
13 younger patients, but you don't really have but a few  
14 patients under 50 that have been studied, that have  
15 been diagnosed. Is there intent in the labeling that  
16 this would be for population with certain risk factors  
17 over the age of 50 or not?

18 DR. DOMURAD: We had not anticipated  
19 putting in an age limitation. We did take all  
20 patients -- the age limitation within the study was  
21 for normal health comparators, where we did say they  
22 had to be 50 or older because, as you've seen, the  
23 majority of patients who are diagnosed with cancer are  
24 older. But that's a majority, it's not categoric.  
25 And when recruiting patients for the study, we did not

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1 put an age limitation other than that they had to be  
2 above the age of consent, they were adults.

3 And there are patients who, I think our  
4 youngest cancer patient ranged, I think, about 18 or  
5 20. So it does occur in younger.

6 CHAIRMAN LADOULIS: Okay, yes.

7 MS. WHEATLEY: I was a little concerned  
8 about the fact that in your summary statement you  
9 talked about the prognosis of a patient with cancer  
10 diagnosed at an earlier age, and we know that when  
11 cancer is diagnosed at an earlier age the expense goes  
12 down. Will there be programs or will patients who do  
13 not have insurance be included in this study? Because  
14 I noticed when you had your clinical slides up, there  
15 aren't too many patients from the population, ethnic  
16 population, that would be in high numbers.

17 So I was just wondering if your data is a  
18 little skewed because you don't have a lot of variety  
19 within those populations.

20 DR. DOMURAD: We were careful to choose  
21 some of our sites that they were in under-served  
22 populations, medically. We chose sites that did have  
23 high minority populations. We also had Veterans'  
24 hospitals that had a high proportion of patients. So  
25 I think actually they are represented. Also, I just

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1 want to note that we're talking about an earlier stage  
2 of cancer, not an earlier age of the patient here, in  
3 our conclusion.

4 MS. WHEATLEY: No, not about age, I was  
5 talking about a stage. Because I think that, you said  
6 it occurred in white men and you pulled the American  
7 Cancer Society stating that it occurred in white men  
8 more than African-American men. Has there really,  
9 really been a study to determine that it does not,  
10 that it does not occur as often in ethnic men as in  
11 white men?

12 DR. DOMURAD: I believe it does.

13 DR. MALKOWICZ: Yes, yes, the general  
14 distribution, it's text book findings, you'll see  
15 that. As to understanding of why that's the case,  
16 because even smoking habits can be similar and  
17 similar, even socioeconomic groups and other groups,  
18 no one has an absolute answer for it, but that is just  
19 the general experience with anybody who's active with  
20 bladder cancer.

21 CHAIRMAN LADOULIS: Yes, Dr. Taube.

22 DR. TAUBE: Yeah, I'd like to go back to a  
23 comment that Dr. Malkowicz made before that relates to  
24 the importance of finding the T-2 Stage or TIS and  
25 anything above that, but particularly those stages.

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1 And the data seem to suggest, and the lower importance  
2 of finding, perhaps, of finding the early stage  
3 relating to the issue of lead time bias and even just  
4 further development.

5 Because the data suggests that the higher  
6 cut off would still have a pretty good sensitivity for  
7 the T-2 to T-4 and the TIS.

8 DR. MALKOWICZ: Right. Yeah, the issue  
9 though is again how comfortable are you with saying,  
10 superficial transitional cell carcinoma. Well, it's  
11 cancer, but maybe it's more of a nuisance disease than  
12 a life-threatening disease and missing those  
13 diagnoses, okay. And when I deal, you know, and  
14 again, are you dealing with populations or are you  
15 dealing with individuals.

16 If a physician dismisses somebody with  
17 bladder cancer or dismisses somebody with hematuria or  
18 some risk factors and then six months later they're  
19 found to have bladder cancer by another physician,  
20 that prior physician is felt as not having reasonably  
21 carried out their duties in terms of fully evaluating  
22 that patient. And you can explain to say, well, a  
23 grade, you know, one, TA lesion has only a five  
24 percent chance of progressing to a muscle invasive  
25 disease, but that's physician talk and statistics talk

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1 and not that you missed cancer in my husband.

2 And that's the difference in terms of what  
3 you're dealing with on a one-to-one basis as opposed  
4 to looking at the big picture in terms of missing or  
5 getting a cancer diagnosis.

6 So I agree that it's sort of where you're  
7 comfort level is in terms of saying, you know, finding  
8 a three centimeter papillary tumor a year later by a  
9 gross hematuria, that's okay. And I don't that, from  
10 our level of training and from where our sensitivity  
11 levels and feeling of prosecuting the findings of a  
12 regular laboratory issues or concern for a patient's  
13 health and being asked to be the person to delineate,  
14 what's your state of health? That's not acceptable.

15 DR. TAUBE: Yeah. It's my understanding,  
16 though, that there is some difference of opinion on  
17 that and in, I heard some data presented from Europe  
18 and so on where they believe in monitoring for a  
19 longer period of time, patients with a T-1 lesion or a  
20 TA lesion.

21 Whereas in this country, there is as  
22 tendency to treat more aggressively. The, in your  
23 summary you indicated that there's no morbidity to the  
24 patient. But in fact if you go in and do cystoscopy  
25 and remove early lesions, there is morbidity for the

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1 patient.

2           And if you treat with, even intra-vesicle  
3 therapy, there is morbidity to the patient. So, I  
4 mean maybe it is an acceptable morbidity, but I'm not  
5 sure that we have data and I would love to hear if  
6 there are data in terms of long-term benefit to TA,  
7 TA/T-1 patients who have a very low probability of  
8 progression.

9           DR. MALKOWICZ: Right. I think first  
10 you'd have to separate out the TAs from the T-1s,  
11 because those of us who are involved in a lot of the  
12 biology of this, the molecular biology, we see T-1  
13 disease as a much, when it's into the T-1, we mean  
14 it's into the lamina propria, not just this mucosal  
15 lesion, not just a wart, but something that's showing  
16 some of the phenotypic characteristics of invasion and  
17 dissemination.

18           Not quite there, but taking its baby  
19 steps. That's a different group. And I think we're  
20 going to have to say T-1, by everyone who does any  
21 research in this area and treats these patients, we've  
22 gotten a heck of a lot more aggressive because we've  
23 found out over the past decade by repeated BCG or  
24 mitomycin therapy in the bladder, you're going in, you  
25 do the cystectomy and they have nodes all over the

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1 place and you've over done it in terms of that.

2 And actually the sentiment, both here and  
3 both with investigators in Europe, is T-1 disease is a  
4 bad disease, that's a shaky disease. But let's look  
5 at T-1, which is still the majority of patients and  
6 keeping that valid. The T-1 disease, essentially what  
7 you're talking about is a sense of attitude of what  
8 you're comfortable with. If you have a more blase  
9 attitude towards a superficial papillary lesion and  
10 that's the societal opinion on it, well that's fine  
11 and what you're willing to accept.

12 At least in my practice and most of my  
13 peer group people in academic and in high quality  
14 community is that when someone comes to the doctor and  
15 they've got blood in their urine and it come mean  
16 cancer, they want you to tell them whether or not  
17 they've got cancer or not. And then they'll sort of  
18 let the chips fall where they may. For most of the TA  
19 lesions, first time around you're not even going to  
20 treat with muscle invasive disease.

21 Sooner or later that would manifest itself  
22 with gross hematuria and whether or not you want to  
23 have that while you're on vacation and have gross  
24 hematuria or have it picked up before it's  
25 significant, again, it's a matter of style and choice

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1 or what you feel comfortable with. And our idea is to  
2 really sort of pick up on these things and see where  
3 it's going earlier. And again, even with TA lesions,  
4 there's some gradation of progression, eight percent,  
5 maybe ten percent.

6 But if somebody isn't well informed of  
7 their potential over life to have a ten percent chance  
8 of the progression for, to muscle invasive disease,  
9 which means removing your only bladder, that's  
10 bothersome to most of the patients that we deal with.

11 So again, it becomes a population versus individual  
12 issue on those issues. And that's where I'd say you  
13 just can't take that.

14 Now in talking about intervals and lengths  
15 of cystoscopy, people are actively investigating that.

16 And say, can we be a little bit easier on how much we  
17 do and that's a very active area of investigation  
18 right now that we're looking at.

19 So those things that you're talking about  
20 are quite accurate. But as to whether or not you can  
21 dismiss the diagnosis, I'd strongly disagree with that  
22 right now, at least in the people that I deal with.  
23 They would take great umbridge to me letting things go  
24 and not really fully evaluating it.

25 DR. DILORETO: I would concur with that.

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1 The standard of care in the U.S. is treatment. And  
2 we're not talking about treatment here, we're talking  
3 about diagnosis and it's two different things. The  
4 other issue is these lesions can present in multiple  
5 fashions and, you know, you can have a TIS, CIS lesion  
6 and have a papillary lesion. You're finding the  
7 papillary lesion, you're not finding the CIS lesion.  
8 And that's a fairly common issue and in fact may be  
9 part of the reason for recurrences because they are  
10 missed initially.

11 And again, this, we're talking about  
12 diagnosis, not treatment. And again, the standard of  
13 care is to treat.

14 DR. KEMENY: But I mean, I like to think  
15 of it as, you kind of, what would you do if it was  
16 you. I mean, and you know, I think most of us in this  
17 country would rather know what the situation is and  
18 then have decisions about the treatment. But the idea  
19 of kind of not knowing, because it might be bad for  
20 you to know, I mean it's just, that's not the way we  
21 do things here.

22 DR. BERRY: This point is really sticking  
23 in my craw, and I beg your forgiveness. As I look at  
24 the sensitivity and specificity of 68 percent and 69  
25 percent or so, they seem low to me. Now that's okay

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1 if we're going to get something out of it.

2 What I'm especially worried about, as  
3 opposed to apparently other members of the panel, are  
4 the false positives. What I see in patients -- not  
5 this scenario but in other scenarios -- is that if the  
6 marker is up they say, "I've got cancer." They don't  
7 understand about positive predictive value, and  
8 neither -- forgive me -- neither do most doctors.

9 If the cancer is up, they treat it as  
10 though it's cancer. If the marker is up, they treat  
11 it as though it's cancer. And I'm worried about that.

12 Is there something that members of the panel can say  
13 or that Dr. Malkowicz or others can say to soothe my  
14 mind?

15 DR. DiLORETO: Can I jump in before --

16 DR. BERRY: Sure.

17 DR. DiLORETO: -- you? The analogy is  
18 PSA. And that, in my mind, takes up 90 percent of my  
19 day-to-day activities versus what this would be doing.

20 This test is significantly better on a sensitivity  
21 issue than what we currently have, which is cytology,  
22 which is poor.

23 Going back to the PSA issues, a PSA of 9  
24 does not mean you have cancer. And I think it's been  
25 an evolution of thinking between the population and

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1 the physicians, at least the better physicians, to be  
2 able to explain to the population that that does not  
3 mean they have cancer.

4 A false positive in this would be the  
5 same, from my standpoint. It doesn't mean they have  
6 cancer. It does mean that the clinician needs to be  
7 very careful to follow that particular patient. And  
8 it's the same thing.

9 DR. MALKOWICZ: The addition that I see to  
10 it is that it's not an isolated test, as a lot of PSA  
11 tests are, too. It's adjunctive, and the guys or gal  
12 already have some blood in their urine or some other  
13 reasons. You know, you've been smoking for 40 years  
14 maybe, or some other issue of that nature. So the  
15 adjunctive nature of it removes that anxiety from it.

16 The fact that they've got a little blood  
17 in their urine, by a lot of people's standard, says  
18 you need to be evaluated, so it's already just, how  
19 intently are we going to evaluate it? What's the  
20 perspective the physician is going to take on your  
21 case? Not the binary or the dichotomous decision of  
22 go on your way or be evaluated. Most of these people  
23 in this study were going to be evaluated anyhow.

24 DR. LADOULIS: I have a similar concern.  
25 You know, I guess I've expressed it. But maybe you

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1 could clarify it somewhat by answering the question as  
2 to why it is that a 10 unit per ml cutoff is  
3 appropriate in monitoring patients with previously  
4 diagnosed disease, so that if they're below 10 there  
5 is probably little evidence of a recurrence. Whereas,  
6 for the diagnosis, as an adjunct in the patient  
7 undiagnosed, you propose that the cutoff ought to be  
8 five.

9 DR. MALKOWICZ: For those already who are  
10 being monitored, they have a transformed urethelium or  
11 lining of their bladder, so there's more background  
12 noise, and there's more issues going on in terms of  
13 abnormalities there. So they're going to be followed  
14 anywhere. They've moved into another paradigm of  
15 followup, and this just kicks in a little bit more.

16 And as we were discussing before, as  
17 people are starting to think about lengthening or  
18 shortening intervals of cystoscopy, and other issues  
19 like that, so that heralding event can be up in that  
20 neighborhood. And also those people -- like we say,  
21 they're in it for the long haul, so maybe a little  
22 movement between five and 10 isn't quite as big a  
23 deal.

24 But here, when you're looking at not quite  
25 incident, because you're not talking about the

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1 screening population but a disease detection  
2 population, that they're already part of a paradigm  
3 where they're getting cytology, which is a highly  
4 specific test. They're going to get imaging of some  
5 sort or one puts it together.

6 So here you don't want to miss things in  
7 terms of sensitivity. And if you just set things up a  
8 little bit too much to drop down to a sensitivity of  
9 50/50, then it's, you know, pick a quarter out of your  
10 pocket, flip a coin, instead of get the test. And  
11 that's why it gets dropped down in that sense.

12 DR. DiLORETO: I would concur. There are  
13 two different populations, and there ought to be two  
14 different levels set for this.

15 DR. LADOULIS: But you also -- they did  
16 present some data in terms of what the predictive  
17 values might be in a population, with different cutoff  
18 values. Can you resummarize that data? I think that  
19 you have the submission in --

20 DR. MALKOWICZ: Yes, we have it here. The  
21 effective analysis, as you go through a range from  
22 four to 10, the predictive value is about 14-1/2, 15  
23 percent. At a level of 10, it doesn't jump up  
24 tremendously, but it is higher at 22-1/2 percent.

25 So you're going from about 14 to 22, about

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1 a seven percent difference, and then the dropoff in  
2 the sensitivity goes from about 70 down to 50. So the  
3 tradeoff one direction for the other, when you look at  
4 it numerically -- and this is what we have in front of  
5 us -- just doesn't seem like you're gaining a heck of  
6 a lot.

7 DR. CARPENTER: I just wanted to echo what  
8 the other panel members have said. My major concern  
9 relates to the false positive rate in clinicians other  
10 than urologists.

11 You know, if a wide range of clinicians  
12 begin to use this, that aren't highly educated,  
13 whether they're going to, you know, properly utilize  
14 the test in conjunction with other tests -- and also  
15 refer at the appropriate time -- in that case, the  
16 sensitivity is good but the false positive rate I'm  
17 really worried about with those non-urology  
18 clinicians. I don't know what more you can propose to  
19 satisfy that.

20 DR. MALKOWICZ: Again, well, you know, all  
21 I can say is, again, that the indication -- it's not  
22 screening. You know, it's just adjunctive and really  
23 aimed more at the evaluating physicians. Sort of the  
24 creep issue is real.

25 I don't know exactly how I could address

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1 that without having more data and seeing how people  
2 behave in that, and I think that's appropriate but in  
3 the confines as sort of the clinical trial, and who  
4 we're looking at, and the guys and the people doing  
5 this, and the people being evaluated -- the guys and  
6 gals -- that it holds true and does add some value.

7 DR. DOMURAD: If I may add to that.  
8 Having looked at a lot of patient charts at this  
9 point, and reviewed a lot of medical information as  
10 part of our monitoring program, primary case  
11 physicians already have access to voided cytology,  
12 they have access to getting imaging done, and they're  
13 not using them.

14 You know, we had over 1,000 patients in  
15 this study, and not once did I see a previous cytology  
16 report or an imaging report that was not ordered by  
17 the urologist. I think primary care physicians are  
18 hesitant to use it because this is not a single  
19 evaluation. An evaluation by a urologist involves  
20 three things, as a general rule -- cytology,  
21 cystoscopy, and upper tract.

22 A primary care physician is not in the  
23 position to either conduct or evaluate all of those,  
24 and the tendency is to refer on.

25 DR. KEMENY: I think it's important to

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1 remember that bladder cancer is not prostate cancer.  
2 I mean, prostate cancer is the most common cancer seen  
3 in men. Bladder cancer is a cancer that is too  
4 frequent, you know, for all of us, but it's still way  
5 under the most common cancers that we usually see.  
6 There's like 26,000 --

7 DR. MALKOWICZ: There's about 50,000 cases  
8 a year, and about 12,000 muscle invasive cancers here.

9 DR. KEMENY: Right. So it's much less  
10 common.

11 DR. DiLORETO: Just as an adjunct,  
12 hematuria equates GU pathology. And that's why these  
13 patients are being evaluated. They're not being  
14 evaluated just for bladder cancer; they're being  
15 evaluated for GU pathology. And as was mentioned, as  
16 a rule -- and I, in 20 years of clinical practice,  
17 basically can count on one hand the number of times a  
18 PCP has tried to evaluate hematuria.

19 You can't do it just with an upper tract  
20 study. You can't do it without having -- combining  
21 some combination of upper and lower tract studies.  
22 And one of the things you're obviously looking for is  
23 bladder cancer, but you're looking for everything  
24 else. And so given, again, back to the labeling  
25 issue, if it's structured as this product as an aid in

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1 the diagnosis of hematuria, I think will almost  
2 preclude it being a screening tool.

3 DR. LADOULIS: Yes, Dr. Hortin?

4 DR. HORTIN: I mean, this test seems like  
5 another example where we tend to be locked into trying  
6 to fit all tests into kind of a binary decision mode  
7 -- a test like this where there are various shades of  
8 gray, where a five doesn't indicate cancer, and a 10  
9 doesn't indicate cancer, but we want to try to fit  
10 them into that. They have to be either positive or  
11 negative, and based on the value to try to force fit  
12 them into that binary decisionmaking.

13 I don't know whether we always serve the  
14 patients best, or the physicians, and it -- I guess  
15 any individual patient does have to be either positive  
16 or negative. So in the individual sense, you're  
17 trying to arrive at the decision.

18 But I wonder whether for some of these  
19 tests where there are not really biologically  
20 extremely well cut -- well-defined cutoffs, there's  
21 lots of overlap between the positive and the negative  
22 populations, whether we would be better served to  
23 maybe put them into low and moderate and high risk  
24 categories rather than always trying to fit them into  
25 kind of a binary mode.

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1                   What would be your comments about that, in  
2 terms of whether that would be perhaps a useful way to  
3 stratify the cutoff values?

4                   DR. MALKOWICZ:    You know, we'd need to  
5 look at some of the data in that sense.  The sort of  
6 drift upwards in the patients without disease sort of  
7 is an area of contention that you'd have to deal with,  
8 and also the lack of the absolute gold standard and  
9 where you feel comfortable.

10                  I think there's a little lack of data to  
11 be able to set those type of criteria just yet, based  
12 on what we have here, anything previous, and other  
13 markers.  And we'll need more longitudinal data and  
14 sort of a hazards analysis to see what goes on over  
15 the long haul to go in that direction.

16                  But I think your insight is absolutely  
17 correct, that it isn't, as I said, a dichotomous  
18 decision and just go yes, no, and go that direction.  
19 But you need more, I think, than is here to be able to  
20 say you're this risk or that risk or the other, mainly  
21 because a lot of the patients with, I said before,  
22 maybe urologic disease but benign disease are popping  
23 up with a finding here.

24                  And exactly how much that relatively  
25 contributes to those values in a particular high, low,

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1 medium risk group of patients needs to be discerned a  
2 little more carefully. But I think the direction is  
3 correct.

4 DR. DiLORETO: I think from a long-term  
5 perspective I would agree. The clinical studies will  
6 dictate exactly how it's going to be used, but I could  
7 guess that, given the scope of evaluations right now,  
8 if you did an upper tract study, and you did this  
9 test, and you found a certain level, you may develop  
10 some methodology where these people wouldn't be having  
11 an office cystoscopic exam because of the finding.

12 The index of suspicion would be so high,  
13 and rather than duplicating two cystos, they would go  
14 directly towards a rigid cysto and biopsy, which may  
15 not be able to be done in the office. Again, these  
16 are just clinical studies as time goes by.

17 But there may be some long-term benefits,  
18 and even some cost effectiveness issues with something  
19 like this.

20 DR. LADOULIS: Any other questions or  
21 comments from members of the panel? Any sponsor  
22 representatives want to make any additional statements  
23 or comments or a summary?

24 If there are no other questions or  
25 comments to the sponsor at this time, maybe it's

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1 appropriate to take a break. And we can adjourn for  
2 lunch early -- and it is now 11:45 -- so that the  
3 schedule, instead of 12:30 we'll adjourn at -- for a  
4 12:00 lunch.

5 We need to reconvene -- we can move that  
6 up? We could move the reconvening with the FDA  
7 personnel presentation at 1:00 p.m. instead of 1:30.  
8 We could move that up a half an hour. And then we  
9 could have open committee discussion then at 2:30, as  
10 scheduled, or move that up a half an hour as well.

11 If there are no other comments or  
12 questions, then we will do that and adjourn now for  
13 lunch.

14 (Whereupon, at 11:48 a.m., the proceedings  
15 went off the record for a lunch break.)  
16  
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A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:05 p.m.)

DR. LADOULIS: All right. Ladies and gentlemen, I think it's now five after 1:00. I think it's time to resume our deliberations on schedule.

Louise, do you have any announcements you want to make?

MS. MAGRUDER: Nothing.

DR. LADOULIS: Okay. Our scheduled agenda for this time is for a presentation now by the FDA personnel on the sponsor's application.

Nina Chace and Dr. Ponnappalli, Dr. Fourcroy, and Dr. Maxim, good afternoon.

MS. CHACE: These are the FDA personnel that worked on this premarket approval application. I was the lead reviewer. Dr. Fourcroy was the medical officer; Murty Ponnappalli, the statistician; and we had some help from Kristen Meier. And the three of us are here today to answer any questions that you might have.

This submission is for the approval of a new intended use of a previously approved test, and the new intended use is to aid in the diagnosis of persons with symptoms or risk factors for transitional cell cancer of the bladder. And for this new intended

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1 use, the proposed cutoff is five units per ml.

2 The previously approved intended use was  
3 to aid in the management of patients with TCC of the  
4 bladder after surgical treatment to identify those  
5 patients with occult or rapidly recurring TCC, and the  
6 cutoff for that intended use was 10 units per ml.

7 Following are some of the previously  
8 approved non-clinical studies in the original  
9 premarket approval application. We had the limits of  
10 detection was 2.1 units per ml. Note that this limit  
11 of detection is very close to the proposed new cutoff  
12 of five units per ml.

13 There were recovery studies, which were  
14 acceptable. The linearity of dilution was acceptable.

15 They studied potentially interfering substances. And  
16 among several of the newly submitted non-clinical  
17 studies, we had a new NCCLS precision study and a  
18 site-to-site reproducibility study.

19 The FDA has four issues to present to the  
20 panel for their consideration. This is the first  
21 issue, and it has to do with the precision of the  
22 test. Data presented in the PMA show that the  
23 reproducibility of the assay may be plus or minus 256  
24 percent around three units per ml, and plus or minus  
25 12 percent at six units per ml. Are these levels of

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1 variation sufficient to justify use of a cutoff at  
2 five units per ml?

3 Here is a summary of the results of the  
4 new NCCLS precision study. Not that the percent  
5 coefficient of variation for within laboratory results  
6 was 12.4 percent with a mean value of 6.3 units per  
7 ml, which is very near to the proposed cutoff of five  
8 units per ml.

9 Here are the overall site-to-site  
10 reproducibility results obtained in a preliminary  
11 familiarization study. These results met the  
12 sponsor's acceptance criteria for reproducibility.  
13 Note that the percent coefficient of variation of the  
14 specimen with a mean of 3.26 is 25.8 percent.

15 This high coefficient of variation was  
16 seen not only over all of the laboratories but also  
17 within each laboratory when the panel -- one specimen  
18 was repeated four times each day for four different  
19 days in each laboratory. These results suggest that  
20 the within laboratory precision may be problematic at  
21 low NMP22 levels.

22 One might say that these levels of  
23 irreproducibility are typical for ELISA tests near the  
24 limits of detection. However, the limit of detection  
25 of the test is not usually so close to the clinically

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1 relevant level -- the proposed test cutoff of five.

2 The sponsor is doing a full NCCLS  
3 precision study at lower NMP22 levels to characterize  
4 and determine the precision at lower levels.

5 So the question then becomes: does this  
6 irreproducibility at lower levels affect patient  
7 results? After each laboratory passed this  
8 familiarization protocol, the three laboratories  
9 performed a site-to-site reproducibility study with  
10 263 actual clinical specimens spanning the entire  
11 reportable range. And this scattergram illustrates  
12 the spread of those 263 samples.

13 This irreproducibility seen at lower  
14 values was also evident in the study of clinical  
15 samples and affected the clinical outcome of patient  
16 specimens. I drew a line at the proposed cutoff of  
17 five units per ml to see how many discrepant results  
18 there were between each of the two labs. So in these  
19 quadrants here will be the discrepant results, and  
20 here was that analysis individually by lab to lab.

21 And you can see when you compare Lab 1 to  
22 Lab 2, the 13 and the 18 are the discrepant results.  
23 Total of 31 for 11.8 percent. And these are at the  
24 five units per ml cutoff. Laboratory 1 versus  
25 Laboratory 3, there were 38 discrepant results, or 14-

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1 1/2 percent. Laboratory 2 versus Laboratory 2, there  
2 were 31 discrepant results, for 11.8 percent of the  
3 total.

4 Now, if you look at the cutoff of 10 units  
5 per ml, you have fewer discrepant results -- 11 or 4.2  
6 percent, Laboratory 1 versus Laboratory 3; again, 11  
7 for 4.2 percent. And Laboratory 2 versus  
8 Laboratory 3, there were 16 for 6.1 percent.

9 And here is a summary slide to illustrate  
10 that, indeed, there is more irreproducibility at the  
11 lowest test cutoff compared to -- at five compared to  
12 10.

13 One of the reasons for this phenomenon is  
14 that in the clinical world one finds more NMP22  
15 results at the lower level. So you can see there are  
16 many more samples down around five than there are  
17 around 10. So that's one thing that causes this  
18 difference in reproducibility.

19 And also, you can see that most of the  
20 populations that aren't -- this is the bladder cancer  
21 population here with the higher levels, and these are  
22 the benigns. These people had no problem that could  
23 be discovered. These are the normal population, and  
24 these are other cancers. And you can see that all of  
25 those have the mean/median right around three. And

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1 there is overlap with the bladder cancers at five,  
2 where there is less overlap at 10.

3 So, in summary, there are two forces that  
4 are at work to cause false results around five units  
5 per ml. The first is the population overlap, and the  
6 second is the irreproducibility of the assay at the  
7 lower levels.

8 And now our FDA statistician, Dr. Murty  
9 Ponnappalli, would now like to say a few words about  
10 the site-to-site reproducibility study.

11 DR. PONNAPALLI: As Nina pointed out, I am  
12 going to talk about site-to-site reproducibility.  
13 There are three sites here, and because the same  
14 sample is used in all of the three sites, we have to  
15 make pair-wise comparisons; that is, is there  
16 reproducibility between the L1 and L2? Is there  
17 reproducibility between L1 and L3? Is there  
18 reproducibility between L2 and L3? We have to examine  
19 these separately.

20 There are three methods to examine these.  
21 One is by testing that the medians of the two  
22 components are equal. The second one is by using  
23 regression methods. I'm going to go through all of  
24 these three in detail. And the third one is by  
25 examining the concordant and discordant pairs.

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1           Let us go to the first one. To compare  
2 the medians, we asked the sponsors to use the non-  
3 parametric Wilcoxon signed-rank test. When that test  
4 is applied between Lab 1 and Lab 2, the p value turned  
5 out to be .0137. Between Lab 1 and Lab 3, the p value  
6 is .0002. Between Lab 2 and Lab 3, it is .0001.

7           So this indicates high irreproducibility  
8 from a statistical point of view. All of the three --  
9 the p values turned out to be so small.

10           However, there are some limitations to  
11 these comparisons because they are really comparing  
12 only the medians, whereas we would like to compare  
13 each pair -- how much they differ within each pair.  
14 So one can use what I call here regression methods.

15           The idea of the regression method is  
16 assume between any two labs, the observations between  
17 any two labs, there is a linear relationship. In  
18 fact, I performed statistical tests. All of them --  
19 all of the linear relationships are excellent.

20           The reason why you see six of the  
21 comparisons here instead of three is for some  
22 technical reason the regression of Lab 1 and Lab 2  
23 could be different from the regression of Lab 2 and  
24 Lab 1. So I had to include both. Similarly, for  
25 Lab 1 and Lab 3 and Lab 2 and Lab 3.

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1           The most significant among these, in my  
2 opinion, is this column and this column. This column  
3 refers to the intercept on the y-axis, intercept of  
4 the regression line. If the two variables coincide,  
5 if two observations coincide, the intercept has to be  
6 zero.

7           And if the two coincide, the slope has to  
8 be one. This is with reference to slope, and this is  
9 with reference to the intercept.

10           You'll notice if, and only if, both the  
11 intercept is zero and the slope is one, only then we  
12 should say there is agreement between the two. You'll  
13 notice from here that the only place where there is  
14 agreement between the two is this is -- this interval  
15 includes zero, this interval includes one. So that is  
16 the only place when both are satisfied. So by and  
17 large, I would say there is no agreement; there is no  
18 reproducibility.

19           The third one is by means of concordance  
20 and discordance. The difference, of course, is the  
21 cutoff point. And the cutoff point is five units per  
22 milliliter. As Nina already showed this slide, this  
23 is the concordance percentage; this is the discordance  
24 percentage.

25           What is new here is I have set up an upper

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1 bound for the concordance percentage. And from there,  
2 of course, 100 minus this will be a lower bound for  
3 the discordance. Let us look at only -- it's  
4 necessary to look at only one of these two columns.  
5 The upper bound for concordance for Lab 1 versus Lab 2  
6 is 92, Lab 1 versus Lab 3 is 89, Lab 2 versus Lab 3 is  
7 92.

8 We did not go all the way to one -- that  
9 is my point -- in running these upper bounds. U.B. by  
10 the way, that would be -- U.B. is upper bound.

11 Okay. The general conclusion from these  
12 three comparisons is that the NMP values are, by and  
13 large, not reproducible.

14 I now hand it over to Ms. Nina Chace.

15 MS. CHACE: So the FDA question for the  
16 panel is: do you think that the proposed choice of  
17 test cutoff of five units per ml is an acceptable  
18 choice? Here are the comparative performance  
19 characteristics of a cutoff of five versus 10 units  
20 per ml?

21 And we have -- just to remind you, the  
22 sensitivity at cutoff of five is about 70 percent;  
23 specificity, 68 percent; predictive value of a  
24 positive is 14-1/2 percent; predictive value of a  
25 negative is about 97 percent; versus a cutoff at 10,

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1 sensitivity, 52 percent; specificity, 86 percent;  
2 predictive value of a positive rises to 22-1/2  
3 percent; and the negative predictive value about 95.8.

4 Now, here are how the predictive value  
5 changes for different prevalences of disease. And you  
6 can see that the predictive value of a positive  
7 increases as your prevalence increases. This is the  
8 actual rate of the study that the sponsor performed at  
9 14-1/2 percent predictive value of a positive. And  
10 the negative predictive value is best at the low  
11 prevalence.

12 As an alternative, should the sponsor  
13 present the performance characteristics of several  
14 cutoffs -- for example, four to 10 -- to alert  
15 physicians that the predictive value of a positive  
16 increases as the NMP22 values increase. In other  
17 words, you can put more confidence in a higher NMP22  
18 value. This would be sort of a receiver-operator  
19 curve type of approach.

20 Now, the last three questions which we  
21 would like the panel to consider -- and you have those  
22 in your packet -- the assay was approved in 1996 for  
23 monitoring previously-treated bladder cancer patients  
24 using a cutoff of 10 units per ml. What is your  
25 opinion regarding establishing a second cutoff at five

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1 units per ml for diagnosis?

2 Do the assay performance characteristics,  
3 which I have presented to you -- reproducibility,  
4 sensitivity, specificity, positive and negative  
5 predictive values -- support a cutoff of five units  
6 per ml versus, for example, 10 units per ml for  
7 diagnosis?

8 And the last issue: would you recommend  
9 that Matritech create a brochure for physicians  
10 presenting test performance at multiple test cutoffs?

11 Does anyone have any questions?

12 DR. LADOULIS: Yes, Dr. Hortin?

13 DR. HORTIN: The statistical evaluation  
14 that showed that the laboratory results were -- for  
15 the different laboratories were different, there was a  
16 high statistical significance. But if I read those  
17 right, the conclusion was that there was essentially a  
18 bias of about .4 or .5 between laboratories, which  
19 quantitatively was not really a very large value.

20 I mean, if you're looking at the bias, it  
21 was highly statistically significant. But you were  
22 saying that, on the average, a different laboratory  
23 gave you a value of about .4 to .5 different, right?

24 DR. PONNAPALLI: Yes. Yes. So are you  
25 asking how we explain it or --

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1 DR. HORTIN: No, I just wanted to clarify  
2 that point that, although you saw a statistical  
3 difference between the different laboratories to, say,  
4 the .001 or .0001 level, that the actual numerical --  
5 the absolute difference between laboratories on the  
6 average was -- if I took your values -- was about .4,  
7 wasn't it?

8 DR. PONNAPALLI: Yes. Now I remember.

9 DR. HORTIN: So --

10 DR. PONNAPALLI: Okay.

11 DR. HORTIN: So through most of the  
12 measuring range, actually the bias between  
13 laboratories is -- say, near the cutoff values, is  
14 well under one standard deviation of the assay  
15 variation. So that bias actually -- it may contribute  
16 a little bit of variation, but would probably not --  
17 probably not a huge different near the cutoff.

18 I mean, the more significant factor is  
19 actually the precision, where I think the standard  
20 deviation was about .7, I think. So the bias that you  
21 saw was about a half of a standard deviation. It was  
22 not very large.

23 MS. CHACE: I think you also have to look  
24 at the range of differences. And even though the  
25 average was small, there were big ranges for each

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1 sample. So that -- so I guess, overall, the error  
2 canceled out. But for each individual patient, there  
3 were larger differences.

4 DR. HORTIN: You probably didn't do that  
5 evaluation restricted to results only near the cutoff,  
6 did you? I mean, those numerically large values are  
7 going to be for the quantitatively large values. I  
8 mean, it might have been of interest to kind of look  
9 between, say, a range of three and 10, or whatever,  
10 and to see -- or somewhere in that region -- to see  
11 what the bias was in that region.

12 DR. DOMURAD: I don't know if it's  
13 possible for us to have the overhead, so that we can  
14 -- it's available, so if there's questions --

15 DR. LADOULIS: Yes, just a moment. After  
16 there will be time for response.

17 I have a question. Can you repeat the  
18 conclusion or I think the statement that the lower  
19 limit of detection you said was what, 3.1? Did you  
20 say the lower limit of detection?

21 MS. CHACE: 2.1.

22 DR. LADOULIS: 2.1. That's the lower  
23 limit of detection of performance of this assay.

24 Then, what is the, you know, significance  
25 of some of the medians which are less than three in

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1 some of the population? What kind of reproducibility  
2 are those medians, if they were to be evaluated?

3 MS. CHACE: The only --

4 DR. LADOULIS: Would it be 25 or --

5 MS. CHACE: -- data we have right now was  
6 that, let's see, the --

7 DR. BERRY: Just to clarify, those are  
8 medians of the differences, is that correct?

9 MS. CHACE: Yes.

10 DR. BERRY: And so it's not surprising  
11 that --

12 DR. LADOULIS: Oh. The medians or the  
13 differences or --

14 MS. CHACE: No, no, no. The only data we  
15 have is this familiarization study where they had a  
16 sample panel at three, around three. And that's  
17 within laboratory reproducibility within --

18 DR. LADOULIS: Well, maybe we could  
19 clarify that at this point, at some point soon. What  
20 is the lower limit of detection?

21 MS. CHACE: 2.1.

22 DR. LADOULIS: 2.1. That's based on the  
23 submission of information, the data, right?

24 MS. CHACE: It's in the package insert --

25 DR. LADOULIS: Okay.

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1 MS. CHACE: -- in the original submission.

2 DR. LADOULIS: All right. So some of the  
3 data, therefore, that had medians that are between two  
4 and three, plus or minus minimal and maximal ranges  
5 many of them, minimal ranges are expressed in decimal  
6 values. Those are meaningless, therefore? They are  
7 below the level of detection, any level --

8 MS. CHACE: I don't think there were any  
9 medians that low.

10 DR. LADOULIS: No, not medians. I mean,  
11 the minimum values, range of values, were presented in  
12 the tables in this data in the submission -- many of  
13 them were medians plus the minimum plus the maximum,  
14 correct? And, therefore, the minimum values that are  
15 less than 2.1 are really below the level of detection.

16 Is that a reasonable qualification to make of all --

17 MS. CHACE: If they're below 2.1, they're  
18 below the limits of detection.

19 DR. LADOULIS: Okay. That's what I wanted  
20 to clarify.

21 DR. BERRY: Would you go to your slide 23?

22 DR. KEMENY: Charles, what does that mean?  
23 Dr. Ladoulis, what does that mean, what you just  
24 said?

25 DR. LADOULIS: Well, in many of the cases,

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1 the ranges of the normals, the benign, these patients  
2 with no urinary tract disease, it's right at or near  
3 the lower limit of detection. And when the minimums  
4 should be expressed as zero, I think they are in the  
5 supplement, is that right? In supplement 2, volume 1,  
6 page 13.

7 DR. BERRY: Dr. Ladoulis, are you talking  
8 about this slide with the median differences? These  
9 are quite small, but that's --

10 DR. LADOULIS: No, no.

11 DR. BERRY: No? Okay.

12 DR. LADOULIS: No. I'm talking about the  
13 actual measurements of units per ml concentrations.

14 DR. BERRY: Okay. All right.

15 DR. LADOULIS: Okay. Go ahead, yes.

16 DR. BERRY: First, just a comment about  
17 Dr. Hortin's statement. My own reading of the  
18 interlab variability here is, though there is a bias  
19 from one lab to another, these reproducibility results  
20 are quite good. I have a question about positive  
21 predictive value.

22 I'm more interested not in the cutoff, but  
23 what the actual value -- what the positive predictive  
24 value is, say, of a five or of a six, or something  
25 between five and 10. We're told that the positive

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1 predictive value, using a cutoff of 10, is 22 percent,  
2 and it's 15 percent for five.

3 But what is it in between? Because that's  
4 the way the test is going to be used as a patient  
5 comes forward with a value of seven, and the question  
6 is, what is the meaning of a value of seven? Do we  
7 have that information?

8 See, this is the cutoff, which if the  
9 cutoff is five it means that you are counting all of  
10 those that are five and above, including 10 and above.

11 What I would like to do is look at between five and  
12 10, or, say, the actual value. What is the  
13 interpretation of that? And I wonder if the sponsor  
14 has that information or if the FDA has that  
15 information.

16 Let me say it again. I believe that what  
17 that says is if you use a cutoff of five, including  
18 everything above five, that's what you get. And  
19 that's not what I'm saying. I want to say suppose you  
20 get a value of exactly seven, what is the probability  
21 that it's actually positive?

22 Or, to combine, if you had the category  
23 between five and seven, what is the probability that  
24 it's actually positive?

25 MS. CHACE: Okay. Well, we have these

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1 distribution charts, but that doesn't speak to just  
2 seven here. But we do have them broken out zero to  
3 five, five to 10, 10 to 20.

4 DR. LADOULIS: These are for values --

5 DR. BERRY: Okay. So I'm interested in  
6 five to 10, and so this tells me --

7 MS. CHACE: Well, this slide was  
8 corrected, so Matritech has the corrected slide from  
9 zero to less than five and less than five to 10. But  
10 it's pretty much similar to this. It's going to  
11 change a little bit.

12 DR. BERRY: I'm losing it here. What is  
13 the appropriate row for the comparison of the 14.5  
14 percent and the 22 percent?

15 MS. CHACE: Let's see.

16 DR. LADOULIS: Could we lower the lights a  
17 little bit, so that we could see the screen a little  
18 better? And a reminder, please, for all participants  
19 to use the microphone -- if you're away from the  
20 microphone -- in any responses, so that the recorders  
21 can transcribe.

22 MS. CHACE: Okay. Here it is for the risk  
23 factor patients -- 700 patients. Here is the bladder  
24 cancers. These are the people who had benign  
25 diseases. And, again, let's see, this needs to be

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1 corrected a little bit. Melodie has the correct  
2 slide. Is this one -- what, do you need it all?

3 DR. TAUBE: Don, were you addressing --  
4 you were addressing the predictive value of a positive  
5 test, not how many --

6 DR. BERRY: Right.

7 DR. TAUBE: -- patients fell in that --

8 DR. BERRY: That's correct.

9 DR. TAUBE: -- difference.

10 DR. BERRY: And so this doesn't address my  
11 question. But if there is -- Mr. Chairman, if there  
12 is a slide that the sponsor has that does address it,  
13 I'd be interested in seeing it.

14 DR. LADOULIS: I think, yes, we'll ask for  
15 that. And, Melodie, I guess you'll present that. Do  
16 you want to --

17 DR. DOMURAD: I'm just moving Dr.  
18 Ponnappalli's microphone. He did not do a cut of the  
19 data that looked at exactly seven or exactly six.

20 DR. LADOULIS: No. But how about between  
21 five and 10?

22 MS. CHACE: I don't think we have the  
23 predictive values for that.

24 DR. DOMURAD: Not the predictive value,  
25 no.

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1 DR. LADOULIS: Okay. All right.

2 MS. CHACE: Any other questions?

3 DR. LADOULIS: Did we satisfy your  
4 question, Dr. Berry?

5 DR. BERRY: No.

6 (Laughter.)

7 But it doesn't seem to be available. But  
8 what I'm concerned about is when you drop down to  
9 five, you're including in that the ones that are 10  
10 and above, which presumably have a higher predictive  
11 value. And the question is: what is the positive  
12 predictive value if you are down near the proposed  
13 cutoff?

14 And it might be quite small, and so we  
15 might be -- this false positive rate will be even  
16 greater for someone who is exactly a five or -- I  
17 mean, exactly a six or a seven or an eight.

18 DR. LADOULIS: If I rephrase your  
19 question, would it be that the question is: what do  
20 you lose by dropping -- you know, by leaving the  
21 cutoff at 10 versus at five?

22 DR. BERRY: Well, no, that we can address,  
23 based on the positive predictive value. But what I'm  
24 concerned about is the patient who actually presents  
25 in the clinic, and he or she does not have a value

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1 above five. He or she has an actual value which may  
2 be above 10, or it may be seven. And if it is seven,  
3 what is the interpretation of that?

4 And when we look at those that are five  
5 and above, we are including, in addition to those that  
6 are seven, we're including those that are 15 and 20,  
7 which presumably have a higher predictive value than  
8 those in the middle. So I'm interested in the actual  
9 value.

10 MS. CHACE: So it's sort of a receiver-  
11 operator curve type approach.

12 DR. BERRY: Well, no, it's not even that.  
13 It's more finely tuned than that. It's the actual --  
14 when a patient gets a reading back, it doesn't say  
15 "bigger than five." It says "seven." And the  
16 question is: what is the interpretation of seven?  
17 How damning is it? And we don't have that  
18 information.

19 MS. CHACE: Well, I'm looking for this  
20 information for every test. So when you figure out  
21 how to do it, we'll be --

22 DR. BERRY: Well, you just look at those  
23 who've got between five and 10, and look at the  
24 positives and the negatives, and calculate the  
25 positive predictive value of being between five and

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1 10. So the data are here. It's just they're not in  
2 the form of --

3 MS. CHACE: What about confidence  
4 intervals?

5 DR. LADOULIS: Well, I had asked -- I  
6 think I had relayed last week a question for the  
7 sponsor as to whether or not you had a distribution  
8 histogram for the 56 patients as well as for those  
9 with benign disease, just the frequency histogram  
10 rather than these whisker plots, what the actual  
11 values are. Is that available? And you will be able  
12 to show that?

13 DR. DOMURAD: Are you referring to the  
14 scattergram that we showed earlier today?

15 DR. LADOULIS: No. I'm talking about a  
16 frequency histogram of 56 patients, and then the other  
17 categories of patients with risk factors. Histogram  
18 of values and of the frequency.

19 DR. DOMURAD: Let me show you --

20 DR. LADOULIS: Okay. If you have --

21 DR. DOMURAD: -- what we have is the  
22 scattergram that we showed -- not the box whisker  
23 plot, but the scattergram, which showed each  
24 individual value.

25 DR. LADOULIS: Okay. If you'd hold onto

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1 that, then I guess we'll -- Dr. Campbell, I think,  
2 from the agency would like to make some comments.

3 DR. CAMPBELL: This is Greg Campbell. I'm  
4 the Director of the Division of Biostatistics. The  
5 question that Dr. Berry is asking is an interesting  
6 one. It's one that the agency -- this center has not  
7 focused on in many other devices.

8 But I think from the table that Nina Chace  
9 had put up, you can figure out for the populations  
10 studied, with the various cutoffs of four to 10. So  
11 if I could ask Nina to bring up that table, I think we  
12 can answer Dr. Berry's question.

13 MS. CHACE: Isn't that Bayesian?

14 DR. CAMPBELL: No, no, no, no, no, no, no,  
15 no, no. It's this table.

16 MS. CHACE: That one?

17 DR. CAMPBELL: Yes. Thank you.

18 If you now look at this table and look at  
19 the cutoffs of five and 10, and suppose you wanted the  
20 positive predictive value for values larger than five  
21 but less than 10, you can see that there are 39 values  
22 above five of the people with the disease, and 29  
23 above 10. So there are 10 between five and 10.

24 And in the specificity column, for the  
25 people that do not seem to have disease, you have 483

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1 using five as the cutoff and 613 using 10 as the  
2 cutoff. And the difference there is 130.

3 So in the range from five to 10, you have  
4 10 cancers and 130 non-cancers. So it's 10 out of  
5 140. And you can do that for each of the intervals  
6 between five and 10. And when you do that, for  
7 example, from five to six, you get two out of 39; from  
8 six to seven, one out of 28; from seven to eight, two  
9 out of 26; eight to nine, four out of 34; and nine to  
10 10, one out of 13.

11 DR. BERRY: So it's about seven percent  
12 overall?

13 DR. CAMPBELL: Yes, I think that's fair.

14 DR. BERRY: Which seems quite low to me.

15 DR. LADOULIS: Low, what?

16 DR. BERRY: In the sense of being a  
17 positive predictive value. In the sense that if you  
18 do get a reading between five and 10, you have about a  
19 seven percent chance of actually testing positive on  
20 the gold standard, which seems low. I mean, it's a  
21 good deal lower than even the 15 percent that we were  
22 presented earlier when you combine all of the tests  
23 that are bigger than five.

24 DR. LADOULIS: Okay.

25 DR. BERRY: So, roughly speaking, the 22

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1 percent at 10 is taken down to 15 percent because of  
2 the lower number, the about seven percent between five  
3 and 10.

4 DR. LADOULIS: Okay.

5 DR. KEMENY: But, again, that's looking at  
6 positive predictive value rather than sensitivity,  
7 because that's bringing in specificity to it. The  
8 positive predictive value is the combination of  
9 specificity and sensitivity.

10 DR. BERRY: Right. But it's putting in a  
11 little bit more than that. It's bringing in the  
12 actual value, which I think is appropriate.

13 DR. KEMENY: No. But the actual value  
14 meaning including specificity and sensitivity. If you  
15 just look at sensitivity, then you need to look at the  
16 numbers that are presented right there.

17 DR. BERRY: Well, if you just look at  
18 sensitivity and specificity, presumably it's for a  
19 particular cutoff. But I want to break up the cutoff  
20 of greater than five into the greater than 10, and the  
21 between five and 10 and ask what the relative  
22 contribution to the positive predictive value  
23 entailed.

24 And what I see is that the contribution of  
25 the greater than 10 is substantial. It's about 22

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1 percent. But the contribution of the between five and  
2 10 is about seven percent. And on the average, it's  
3 about 15 percent.

4 DR. KEMENY: No, I understand what you're  
5 saying. But what I'm saying is -- and what I think  
6 they explained was -- that the positive predictive  
7 value isn't quite as important to them because  
8 specificity is not so important because they have  
9 specificity with other means, like cytology, whereas  
10 on this test they're relying on sensitivity.

11 They're opting to pick a higher  
12 sensitivity point -- that's why they're picking five  
13 -- rather than a higher PPV -- a positive predictive  
14 value -- because they want to go for a higher  
15 sensitivity because the specificity they're going to  
16 leave to the other test, because this test is going to  
17 be used in conjunction with other tests, not as a  
18 stand-alone test.

19 DR. LADOULIS: Well, perhaps another way  
20 of looking at it, as I look at the data, is, in fact,  
21 if the cutoff value were four instead of five, it  
22 would be the same. Sensitivity is 39; there's 39  
23 patients. So this, you know, does not seem to be a  
24 significant loss or -- you know, even if there were  
25 six, these two patients that are missed supposedly of

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1 the positive group here, of the 56.

2 So the question is: where is the, you  
3 know, appropriate clinical threshold going to be? Is  
4 it to err on the side of having false positives, or is  
5 it to err on the side of uncovering, you know,  
6 diagnostically positive tumors in at risk patients?

7 DR. DiLORETO: Getting back to what I said  
8 a while ago, false positives aren't bad, I don't --  
9 clinically. This has to be gotten out, assuming there  
10 is an approval and some labeling issue, you can't  
11 muddy the waters. I mean, I'm a clinician, and 20  
12 years ago I went to sleep listening to statistical  
13 analyses.

14 (Laughter.)

15 I managed to stay awake today. But you  
16 can't do this to the clinicians. You have to set some  
17 levels for which they are used to using any particular  
18 product and let the outcomes and let the analyses fly  
19 -- and post-marketing studies or clinical studies.  
20 What we're going for is sensitivity, I think  
21 personally.

22 The false positives are not going to harm  
23 anybody because they are going to be getting the same  
24 evaluation. You're trying to pick up lesions, and  
25 you're trying to maybe, as things evolve, change the

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1 process with which those lesions get worked up, not  
2 what this PMA is about, but I'm just saying clinically  
3 over the long haul.

4 Leaving it at 10, which is where it was  
5 for the monitoring study, and placing it at five for  
6 the diagnostic study, I think is a good choice; again,  
7 based on sensitivity issues.

8 DR. BERRY: I'm really confused because, I  
9 mean, if false positives don't matter, then why don't  
10 we just use a zero? Why do we even use the test? Why  
11 don't we do these other tests and decide whether or  
12 not the person has cancer?

13 DR. DiLORETO: I think they mean  
14 something. Like I said before, these patients are  
15 going to be evaluated. If I do a cysto and an upper  
16 tract study on somebody that has an atypical cytology,  
17 which is what I would -- the analogous situation being  
18 a false positive, I'm going to do more, I'm going to  
19 look more, do other things, trying to find the  
20 problem.

21 If, as an example with this, the test is  
22 positive at five, and I do a negative upper and lower  
23 tract evaluation, personally, I'm not going to let  
24 that ride. Something more has to be done. That's a  
25 false positive. But maybe it isn't a false positive.

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1 Maybe those patients should be looked at differently  
2 or further studies be looked at in that particular  
3 group of patients.

4 DR. LADOULIS: I think it's helpful, as a  
5 reminder, that, you know, the FDA, and the agency, and  
6 certainly not this Advisory Panel, is in the role of  
7 defining the clinical practice of medicine, and that's  
8 even a statutory denial on the FDA's -- it's in the  
9 statutes.

10 What this whole body of deliberation  
11 today, and the whole agency role, is in regulating  
12 commercial marketing of a product. And so it has to  
13 do with what the claim is and the representations of a  
14 product, not about practice.

15 And so I think that distinction needs to  
16 be kept in mind. The clinicians will use tests as the  
17 judgment. And the question is, ultimately, at the end  
18 of the day today, what is the recommendation of this  
19 Advisory Panel to the agency as to what is the claim  
20 that a company can make for the introduction into the  
21 marketplace of a product? And I think that that's a  
22 fair statement.

23 Erika?

24 DR. AMMIRATI: Thank you. Just as I was  
25 sitting here squirming, I was about to say just that.

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1 And we can get into an endless loop of, "Well, I  
2 would use it like this," and "I would use it like  
3 that." And that's very valuable. But if we look at  
4 the responsibility of the sponsor, is to come here  
5 with data to support a claim, and to look at the best  
6 performance characteristics that we have.

7 And if we take it in context as an  
8 adjunctive test, that if you're counting on cytology  
9 as the gold standard to be your specificity of 100  
10 percent, why not maximize the sensitivity to get a  
11 more rounded view of it? And it looks like the five  
12 cutoff does that, where you get the maximum amount of  
13 sensitivity and maybe let your cytology take care of  
14 the specificity, with the understanding that you will  
15 get some false positives at that.

16 And for some of the reasons we discussed  
17 this morning, again, the practice of medicine and  
18 whether that causes anxiety and how doctors handle  
19 patients with that, those are real issues, but beyond  
20 what we have here in terms of the performance  
21 characteristics.

22 DR. BERRY: Just one follow up. The point  
23 that maximizes sensitivity is zero. It's not five.

24 DR. AMMIRATI: Within reason. I amend my  
25 statement.

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1 (Laughter.)

2 DR. LADOULIS: Yes. Well, at a level of  
3 five, it is two out of three patients, or 66 percent,  
4 are identified. At a level of 10, one out of two.  
5 That's acceptable.

6 But the performance characteristics in  
7 terms of reproducibility have been discussed here.  
8 You've presented -- and I think Dr. Berry has alluded  
9 to that -- the fact that the reproducibility may be  
10 satisfactory.

11 DR. KEMENY: I just want to say again,  
12 from a clinical point of view -- I mean, if you have a  
13 test -- I mean, just putting it into kind of, you  
14 know, layman's terms, there's a 50/50 chance that it's  
15 worthwhile, that it's positive, versus an almost 70  
16 percent chance that it's positive. That makes a big  
17 difference. I mean, basically, a 50/50, you know,  
18 chance is -- you might as well just flip a coin.

19 DR. LADOULIS: Right. Any other comments  
20 from staff? Any other suggestions or any questions  
21 from the panel?

22 DR. HORTIN: I have a question. I have  
23 been looking through trying to decide exactly how the  
24 testing procedures were performed. It wasn't clear to  
25 me whether all of the analyses were for individual

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1 subjects. Were they done singly or in duplicate? I  
2 was trying to look through, and I didn't see in your  
3 package insert or other places describing exactly how  
4 that was done. So I was just wondering, because it  
5 would have a fair impact on the precision of  
6 measurement.

7 MS. CHACE: The package insert says to do  
8 it in duplicate.

9 DR. HORTIN: Oh, it does? Okay.

10 MS. CHACE: I don't know what was done.

11 DR. DOMURAD: It was done.

12 MS. CHACE: So this is reproducibility. I  
13 don't know how the analysis -- the NCCLS analysis I  
14 think says do it in duplicate.

15 DR. DOMURAD: Yes, it does.

16 MS. CHACE: How about the four by four  
17 repeats? Were those duplicates? So that was two  
18 duplicates.

19 DR. DOMURAD: I'm looking to --

20 DR. HORTIN: Each individual patient value  
21 is average of the duplicate measurement. Okay.

22 MS. CHACE: That's what the package insert  
23 says to do.

24 DR. LADOULIS: Nina, are there any other  
25 comments that you'd like to make? Any other questions

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1 from the panel before we give the floor to the  
2 sponsor?

3 I think now is the appropriate time, then.  
4 Is there some response that you'd like to make, or  
5 any clarifications you'd like to make in regard to the  
6 questions that were raised, and concerns that have  
7 been raised in doing this presentation?

8 DR. DOMURAD: I would make only one  
9 response at that point. The --

10 DR. LADOULIS: Please use the microphone.  
11 Close the --

12 DR. DOMURAD: I'm trying to get closer to  
13 it. Thank you.

14 The CVs that were discussed at a mean  
15 value of 6.3, the standard deviation as about 0.78  
16 with a CV of 12.4 or 6. When we looked at the mean  
17 concentration of 3.26, please bear in mind that that  
18 was not done to NCCLS standards, and that is being  
19 done now. But the value that was put up was from  
20 familiarization testing -- a different protocol.

21 But there again, the standard deviation as  
22 0.84. So the standard deviation, the absolute measure  
23 of difference, was very close -- between 3.26, which  
24 approximates the medians of those patients in the  
25 study who did not have cancer, to the 6.3, which

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1 approximate the medians of -- or the cutoff value of  
2 the patients for sensitivity.

3 DR. HORTIN: I have a question.

4 DR. LADOULIS: Yes, Dr. Hortin?

5 DR. HORTIN: When the assay was originally  
6 designed, was it set up to try to optimize  
7 sensitivity? Or was it set for a particular measuring  
8 range? Since it performs optimally at about 30 or 40,  
9 and you're now trying to apply it for a measuring  
10 range where it doesn't really perform very well, is  
11 that a fundamental limitation of the assay that you  
12 can't make perform any better? Or was it just that  
13 you set that up originally because you thought the  
14 measuring range was going to be like 10 to 50 or --

15 DR. DOMURAD: There is some limitations to  
16 the technology.

17 MS. CHACE: What about a lower calibrator  
18 lower than 7.5 units per ml?

19 DR. DOMURAD: That's something we'd be  
20 happy to discuss. Lowering that lowest calibrator is  
21 a possibility.

22 DR. LADOULIS: Any other responses from  
23 Dr. Malkowicz or -- okay. Any other questions from  
24 the panel?

25 If there are no other questions, then it

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1 brings us to the time for a 15-minute break, because  
2 we will reconvene in about 15 minutes and begin our  
3 open committee discussion and review and  
4 recommendations. Do we want to do that or -- let's  
5 reconvene in just -- we could have the open public  
6 session without a break.

7 (Laughter.)

8 How is that sitting with everybody? It's  
9 now five minutes to 2:00, and we can begin in just  
10 about three minutes. Okay?

11 Thank you. Thank you, Nina.

12 MS. CHACE: Should I turn this off or --

13 DR. LADOULIS: I guess you can turn that  
14 off.

15 MS. CHACE: Do you think you'll need any  
16 more slides or anything?

17 DR. LADOULIS: Just take a breather, and  
18 then we will go right into the open session without a  
19 break.

20 Before we begin the actual open session, I  
21 just have to make an announcement that if there's  
22 anyone who wants to make a -- anyone from the public  
23 who wants to make a comment or a presentation, this is  
24 the time in which to make it, during this open  
25 session. If there are none, then we will -- let's go

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1 without a break.

2           Okay. We're going to begin now without a  
3 break to -- you want a break?

4           ALL: No.

5           DR. LADOULIS: No break. We're going to  
6 begin our open public discussion, and we're going to  
7 go around the table for any comments, summary  
8 comments, questions, concerns, recommendations. And  
9 after we conclude and get exhausted from that, and  
10 have exhausted all of our concerns and questions,  
11 there will be a break. And that will be followed by a  
12 presentation from Louise as to how the panel is to  
13 vote and the instructions as to what is to be made as  
14 far as recommendations.

15           We have, then, this final session after  
16 the break in which we will have to consider separately  
17 all conditions, as well as specific recommendations,  
18 if any of the panel want to make such conditions. And  
19 so that may take a little more time than a lumping of  
20 issues.

21           All issues of concern and that give rise  
22 to any recommendations that you want to make to append  
23 to the recommendations of the panel have to be  
24 separately discussed, voted, and then proceed to the  
25 next.

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1           Okay.     So let's begin now with some  
2 discussions around the table. I think I'll put the  
3 burden on the clinicians and the staff and begin going  
4 around the table from Dr. DiLoreto's side of the table  
5 over here, and Dr. Kemeny, and go on. Would you like  
6 to start?

7           DR. DiLORETO: I will start and be very  
8 short. I think that I'd like to commend the sponsors.  
9 I thought it was a well done study and well put  
10 together and well analyzed. I would concur with the  
11 level that has been suggested. I think that this is a  
12 complement to the existing standards of evaluation --  
13 will be added to from a clinical standpoint.

14           My only issue would be -- and I'll say it  
15 now and maybe repeat it later -- that the labeling  
16 have something in the vernacular of stating that it be  
17 used in conjunction with, and not in lieu of, current  
18 existing standards of evaluation of patients that are  
19 at high risk for developing these tumors. And I'll  
20 leave it at that.

21           DR. LADOULIS: Dr. Kemeny?

22           DR. KEMENY: I agree with what Dr.  
23 DiLoreto said. I also think that this is -- the  
24 sponsor has done a good job on this, and I think this  
25 is going to be a step forward for helping us diagnose

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1 people with bladder cancer. And I'm happy to see it  
2 come on the market.

3 DR. LADOULIS: Okay. Dr. Petrylak?

4 DR. PETRYLAK: I concur with my two  
5 colleagues that this was a well designed study, and I  
6 certainly think that this will have use. And I also  
7 agree that we should write that it should be done in  
8 conjunction with standard diagnostic tests but not in  
9 substitution for that.

10 DR. LADOULIS: Okay. Dr. Carpenter?

11 DR. CARPENTER: I also agree. The only  
12 concern that I have is in regard to the precision --  
13 at the lack of precision at the lower level, in that,  
14 you know, if you would take the worst-case scenario,  
15 with the CV of 25 percent -- and, let's say, you got a  
16 value of four -- that could push you up to a value of  
17 five, which, you know, that concerns me a little bit.

18 Although I do concur that clinically we do  
19 want to make sure we have -- we maximize sensitivity  
20 and assure that the labeling recommends additional  
21 tests, in which case hopefully that will -- will take  
22 care of the majority of the times when that might  
23 occur.

24 I don't really know how to resolve that  
25 because I don't think it necessarily justifies raising

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1 the cutoff. But I do have some reservation about  
2 that.

3 DR. LADOULIS: Dr. Berry?

4 DR. BERRY: I agree with the conjunction  
5 with, and not in lieu of, and that, I must say, allays  
6 some of my -- the problems I have. With respect to  
7 the issue of five versus 10, I feel very strongly that  
8 it should be done, for the reasons that were indicated  
9 by the FDA in their presentation and for my own  
10 attitude toward false positives.

11 DR. AMMIRATI: Just one brief comment on  
12 precision. I'm glad Dr. Carpenter reaffirmed my  
13 math, because I was afraid in my med tech days I had  
14 forgotten this. But even at a 25 percent CV, which is  
15 as high a CV as we saw with any of the testing -- and,  
16 again, the EP5 NCCLS protocol is still in process --  
17 but at a true three, you're going to run between 2.25  
18 and 3.75.

19 So in the worst possible case, a three is  
20 still somewhat away at 3.75, and, of course, a four  
21 would be closer to five, because now you're at 4.75.  
22 But that's true with any cutoff. You're never going  
23 to be exactly on one side or the other, and everything  
24 has to be looked at in conjunction with other  
25 diagnostic markers.

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1 DR. LADOULIS: Who's next on the panel?

2 MS. WHEATLEY: No comment.

3 DR. LADOULIS: Okay. Dr. Taube?

4 DR. TAUBE: I've really been struggling  
5 with the cutoff. I absolutely agree -- first of all,  
6 I also want to compliment the sponsors because I think  
7 this is one of the larger studies, clinical studies  
8 that I've seen since I've been on the panel. And so I  
9 thought it was pretty well designed.

10 And I definitely concur with the idea that  
11 this has to be done in conjunction with other tests,  
12 other standard tests. But I've been struggling with  
13 the cutoff issue, and I was leaning toward Dr. Berry's  
14 position, going for the higher cutoff. And I just  
15 looked at page 19 of volume 1 of supplement 2, where  
16 it shows the values for the different tumor stages.

17 And I don't think that raising it to 10 is  
18 going to get us any place because the median for the  
19 T0 stage was 13.7. The median for TA is 6.1. There  
20 is no -- and, really, when you get into the higher  
21 stages and some odd median values, the sample size  
22 isn't large enough to say anything about it.

23 So I'm not sure that raising the median  
24 value, or raising the value that you have to find, is  
25 going to accomplish what I also would like to

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1 accomplish, which is to have fewer false positives.  
2 So I think I probably would have to go with leaving  
3 it, as the sponsor requests, at five.

4 DR. LADOULIS: Dr. Hortin?

5 DR. HORTIN: I think as a general rule, in  
6 terms of trying to come up with a screening test, you  
7 want to optimize sensitivity in terms of detection,  
8 and sometimes you weren't interested -- or at least  
9 trading off for specificity a little bit.

10 But I do have a little bit of a problem  
11 for this particular test in terms of using a cutoff of  
12 five, in that I don't feel that it is -- that the  
13 values are particularly reliable there. And you can  
14 do all of the statistical analysis that you want, and  
15 if you get a patient value of five, then all you're  
16 really saying is that the value has a 95 percent  
17 confidence interval of being somewhere between about  
18 3.5 and 6.5.

19 It says that for that individual value --  
20 I mean, you have a relatively large uncertainty. And  
21 I think it's always hard to know how this will vary in  
22 terms of real-world practice. I think usually the  
23 studies are performed under somewhat more ideal  
24 conditions. If you look at the performance of these,  
25 the absorbance values that are generated at -- near

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1 the cutoff value are quite low. They are going to be  
2 more prone to procedural errors.

3 The lowest calibrator value they have is  
4 -- that actually contains the material is 7-1/2. It's  
5 significantly above what the cutoff value is. So I  
6 don't feel that you could have great confidence and  
7 reliability on a value of five, and I don't think that  
8 it would be well placed to have a cutoff value when  
9 you cannot reliability determine what those values  
10 are.

11 So I think that it's a little bit  
12 different than what you're generally trying to  
13 accomplish in a screening assay, but I would propose  
14 either -- I would recommend they either use a cutoff  
15 of 10, where I think you can provide reasonably  
16 reliable values, or to come up with an intermediate  
17 zone somewhere in the middle.

18 DR. LADOULIS: Okay.

19 DR. BERRY: Can I follow on that?

20 DR. LADOULIS: Yes. Dr. Berry?

21 DR. BERRY: Maybe in the spirit of  
22 compromise.

23 Dr. Hortin suggests an intermediate. If  
24 you look at the sum of sensitivity and specificity, it  
25 reaches a maximum at seven, which is an intermediate

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1 value. It's 141 there. At five, it's 137.3, and, at  
2 10, it's 137.8. So maybe, in the spirit of  
3 compromise, we could consider it an intermediate  
4 value.

5 DR. LADOULIS: Well, I hadn't made any  
6 additional comments. I wanted to compliment the  
7 sponsor on a nice presentation, but I still have the  
8 same concerns I think that I have expressed -- that in  
9 the name of improving the pickup of these tumors,  
10 which have a low prevalence and have difficulties in  
11 management, I think that the choices of the cutoff  
12 seems artificially low.

13 And it may have an adverse consequence in  
14 that if the experienced clinicians becomes that -- as  
15 it's used more widely it comes out to be meaningless  
16 and has an effect on the marketplace, that clinicians  
17 may have less confidence in the test as the future  
18 goes on, it may have an adverse consequence as it  
19 might have been intended.

20 I think the suggestion that Dr. Berry  
21 raised is one that I had thought of, but it is  
22 something that has not been proposed or recommended by  
23 the sponsor, unless they want to make some amendment  
24 in the future. So what we're left with is making some  
25 recommendation based on what has been submitted.

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1           And my only reservation is the low level  
2 of this cutoff, which is not far from the limit of the  
3 test.     Secondly, as Dr. Taube pointed out, the  
4 patients in the positive population that have been  
5 assayed with either T0 or even IS or higher grade  
6 lesions have -- median values are all well above the  
7 median cutoff.

8           Nevertheless, in that population of 56  
9 patients, I would -- I mean, I'm pointing out to  
10 myself, as well as to the members of the panel, a  
11 number of those patients come out with values of two,  
12 three, four, that clearly are patients who have  
13 malignancy and have values below the median cutoff.  
14 And that would be a -- those would be false negatives.

15           So I consider it a dilemma, but I think  
16 that the test has sufficient reproducibility and it  
17 probably would be a valuable adjunct in the diagnosis  
18 of a very difficult disease.     And one of the  
19 advantages out of restricting this to the claim that  
20 it be used in an at risk population with patients with  
21 hematuria that are being evaluated is that the  
22 prevalence of this rate for this population is not  
23 seven percent, but it's a much -- a greater  
24 population.

25           And so if you wanted to calculate, I

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1 guess, the positive predictive value in a subset of  
2 the population who present with those kind of  
3 symptoms, talking about somewhat more value that's  
4 added to this test.

5 That's the only comments I have to make.

6 Are there any other second thoughts,  
7 comments, from any others on the panel? Dr. Hortin?

8 DR. HORTIN: Just one other comment. I  
9 think from the standpoint of a clinical study on  
10 things, I think that the study was relatively well  
11 performed, and they kind of did a relatively large  
12 study on things. But I think part of the problem here  
13 is that they were basically trying to apply an assay  
14 which functionally does not perform very well for this  
15 intended application.

16 It's always a lot of work to go back and  
17 kind of start from scratch and reformulate. They  
18 basically should have, ideally, had an assay that  
19 would perform well in this range. And maybe there are  
20 fundamental technical limitations kind of preventing  
21 further improvement in things.

22 But for the intended use, it would have  
23 been much preferable if they could have had an assay  
24 that would have a lower limit of detection and would  
25 have had higher precision in the intended range. This

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1 assay performs very well, probably around 20 to 40  
2 range.

3 But they're trying to push it for an  
4 application where it doesn't really perform very well,  
5 and there might be other ways in terms of  
6 standardizing their measurements in terms of urine  
7 concentration or other things that might have had  
8 further improvement, like they would for other  
9 analytes.

10 So I think it is just a little bit  
11 unfortunate. I think that potentially it looks like a  
12 promising marker and something that will be of use in  
13 the future. I would just hope that at some point for  
14 these applications they would be able to kind of  
15 further optimize and kind of develop the performance  
16 characteristics that would best serve the patient  
17 population with diagnostic applications. They have  
18 kind of a suboptimal assay for this application, I  
19 think.

20 DR. KEMENY: I'd like to respond to that.

21 I mean, you know, it seems to me often when we come  
22 here -- I mean, this is what we have. Yes, it would  
23 be great if we had something that was at 100 percent,  
24 you know, positive for predictive value. That would  
25 be great. If somebody would know about that, we would

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1 pass that right away.

2 I mean, but this is what we've got. And,  
3 you know, and for what it is, I disagree that it's not  
4 that good. I mean, it's the best that we've got.  
5 It's better than cytology. I mean, and that's the  
6 best that we've got up to now. So, I mean, it's a lab  
7 test that's better than another kind of even, in some  
8 ways, more specific lab tests. So I think that  
9 actually -- from a clinical point of view, that's  
10 pretty remarkable.

11 And as far as the cutoff, Charles, I think  
12 you misunderstood what Sheila said, because -- I mean,  
13 and Sheila can correct me -- but, I mean, when you  
14 look through about the stages, if you pick 10 as the  
15 cutoff, you're going to be missing a few of the tumor  
16 types. TA has a median of 6.1. So --

17 DR. LADOULIS: Yes, that's the only one.

18 DR. KEMENY: Right.

19 DR. LADOULIS: That's right.

20 DR. KEMENY: That's the only one, yes.

21 DR. LADOULIS: The exception for that --  
22 all of the others. But those are medians, and that  
23 doesn't --

24 DR. KEMENY: I know.

25 DR. LADOULIS: -- need to be a clinical

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1 issue that we have discussed.

2 DR. KEMENY: I mean, but the point --

3 DR. LADOULIS: There will be half of those  
4 patients who are below.

5 DR. KEMENY: The point is to pick a --

6 DR. LADOULIS: Right.

7 DR. KEMENY: -- clinically significant  
8 spot, so that when you get something that's above that  
9 spot -- not five, but above five -- that, you know,  
10 that means something.

11 DR. BERRY: What does it mean? My  
12 understanding is that the prevalence in this  
13 population of true positives is seven percent, is that  
14 right? Seven and a half percent? And Dr. Campbell  
15 helped us with a calculation which shows that the  
16 probability of true positive, if you are between five  
17 and 10, is seven percent, which means to me that this  
18 test is non-informative. It contains no information  
19 if it's between five and 10.

20 DR. LADOULIS: Do you want to address that  
21 question?

22 DR. KEMENY: I don't understand. I don't  
23 get that. I don't understand what you're saying. If  
24 someone has a value of eight --

25 DR. BERRY: If someone has a value between

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1 five and 10, any -- just take the set of patients who  
2 have values between five and 10, and ask for the  
3 probability that they are positive, true positives.  
4 That is, indeed, the prevalence in the population --  
5 seven percent --

6 DR. KEMENY: But that --

7 DR. BERRY: -- which means to me that the  
8 test in that range has no value whatsoever.

9 DR. LADOULIS: This is alone. The  
10 prevalence that you record -- about seven percent --  
11 is for the population of undiagnosed bladder cancer.  
12 And I think what I've tried to mention is that we're  
13 -- if this test is approved for the use as an aid in  
14 the diagnosis of patients who are at risk because of  
15 the three risk factors, or have at least one of those  
16 risk factors -- or they weren't being worked up for  
17 hematuria, I'm sorry, that's the claim -- this  
18 population is a much smaller subset of the  
19 prevalence --

20 DR. TAUBE: No.

21 DR. LADOULIS: Is that right?

22 DR. TAUBE: I thought that the 7.3 percent  
23 was the prevalence in the at risk population.

24 DR. LADOULIS: Okay.

25 DR. TAUBE: Is that correct?

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1 DR. LADOULIS: What does the 7.3 percent  
2 prevalence rate represent?

3 DR. DOMURAD: The 7.3 is the average  
4 incident rate in this population. The incident rate  
5 went as high as 15 percent in some -- at some of the  
6 sites -- VA hospitals, for example -- which addresses  
7 exactly what you're saying.

8 If you have a population that is  
9 particularly at risk, the incidence tends to be  
10 higher. 7.3 percent was the average across all the  
11 sites.

12 DR. TAUBE: Of the at risk --

13 DR. DOMURAD: Of the at risk population.

14 DR. TAUBE: -- the at risk population, the  
15 ones who --

16 DR. LADOULIS: Okay. All right. So seven  
17 percent of only the at risk population. Sorry.

18 DR. DOMURAD: No, that's the prevalence.

19 DR. LADOULIS: That's right.

20 DR. DOMURAD: That's seven percent of all  
21 of the patients who came in with risk factors were  
22 diagnosed with cancer. That's not positive predictive  
23 value; that's the incidence rate.

24 DR. KEMENY: The incidence from five to --

25 DR. TAUBE: No. Of all of the patients at

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1 risk who had micro hematuria or other risk factors.

2 DR. KEMENY: Okay.

3 DR. LADOULIS: Only seven percent of  
4 those, okay. All right. Okay. So that comes back to  
5 Dr. Berry's comment.

6 So only seven percent of those at risk are  
7 positive.

8 DR. TAUBE: Had cancer.

9 DR. LADOULIS: Are positive for cancer.  
10 That's right. Only seven percent of those turn out --  
11 those 56 patients represent seven percent of a  
12 population all of whom were at risk and were being  
13 evaluated with cystoscopy, cytology, and X-ray.

14 DR. KEMENY: But that was the population  
15 that actually had cancer. So basically, out of 100  
16 people, only seven of them had cancer. That doesn't  
17 mean anything about the test. That's just telling you  
18 what the population is that is at risk for cancer. Is  
19 that correct?

20 DR. LADOULIS: Of the patients with  
21 hematuria, yes.

22 DR. KEMENY: Yes. That's just telling us  
23 that -- that's going back to what I said, which is  
24 that bladder cancer is not all that common. I mean,  
25 so -- I mean, but that doesn't mean anything about

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1 what --

2 DR. LADOULIS: Dr. Berry's comment, as I  
3 understand it -- not just to rephrase it -- to bounce  
4 this back, is that if the population at risk that's  
5 being evaluated, only seven percent probability that  
6 there's cancer, what is the improvement of having the  
7 test in which the value might be six or seven or  
8 eight? Somewhere between five and 10 units per ml.  
9 How does that improve your diagnostic capability in  
10 terms of uncovering or disclosing these patients?

11 DR. AMMIRATI: I think the answer to that  
12 is it gets two out of three, all of the ones that  
13 cytology missed.

14 DR. DiLORETO: Yes, this is a clinical  
15 issue. This is not a statistical issue.

16 DR. LADOULIS: Okay.

17 DR. DiLORETO: This is a clinical issue  
18 because the existing tests that we have are not 100  
19 percent. And you can do a cytology, and it will be  
20 negative. You can do a cysto, and it will be  
21 negative. And you can still have bladder cancer.

22 If your additive with this -- it minimizes  
23 the chances of missing, from a clinical standpoint --  
24 getting back to everything that I said before, it's an  
25 adjunct to what we're doing that I think is clinically

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1 beneficial to the patients. And that's all we're  
2 talking about.

3 DR. LADOULIS: So the comments, then, that  
4 were raised would only affect tests that were being  
5 used to screen alone.

6 DR. DiLORETO: It should never be used as  
7 a screen alone. That's my comment about the initial  
8 labeling or the beginning of our go-around here, that  
9 it be used in conjunction with, and not in lieu of,  
10 standard diagnostic tests in the workup of micro  
11 hematuria, micro/macro hematuria.

12 DR. KEMENY: And I think all of us are --  
13 you know, on the clinical side of things are agreeing  
14 with that -- that it shouldn't stand by itself, but as  
15 an adjunct it's useful. But only in patients at risk.

16 DR. BERRY: I agree with that, too, if  
17 it's bigger than 10.

18 But, Dr. DiLoreto, if a patient comes into  
19 your office and you decide that she has a seven  
20 percent chance of having cancer, and you do a test and  
21 you get the result, and you decide after the test  
22 result that she has a seven percent chance of having  
23 cancer, the test didn't add anything. I'm not talking  
24 about bigger than 10. I'm talking about between five  
25 and 10.

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1 DR. DiLORETO: If it's additive from a  
2 clinical standpoint, in the situations which occur  
3 quite commonly that patients are evaluated, and they  
4 have a negative evaluation, which is -- it happens  
5 very frequently. They have negative cystos because of  
6 the way we're directed to do cystos nowadays, and they  
7 have negative cytologies because of the inadequacies  
8 in the interpretation of that test as it exists across  
9 the country in non-tertiary care hospitals.

10 And even if it's seven percent -- you  
11 know, if you're finding seven percent more, if you're  
12 finding a few percent more, you're picking up cancers  
13 in these patients that would have been missed and have  
14 the potential to go on to more aggressive,  
15 progressives types of lesions.

16 It's not a huge number, but clinically  
17 it's beneficial. I think it's very beneficial.

18 DR. BERRY: That's an important point. If  
19 you're saying that you get additional information from  
20 the patient about the patient, and it turns out that  
21 she has negative characteristics and the probability  
22 of cancer actually lowers on the basis of those  
23 characteristics, and then you do the test and it comes  
24 back up to seven percent, that, of course, would be  
25 valuable. But I don't think we've been presented with

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1 any data that that is the fact.

2 DR. TAUBE: Yes. And the issue also is  
3 that what you're saying is then you look at this test,  
4 which has a very low predictive value of positive,  
5 that it's truly positive, and you're saying because  
6 you have this test you're going to keep looking and  
7 keep looking. That increases the potential for  
8 morbidity and risk as a result.

9 I mean, it decreases the safety factor of  
10 this test, because you're using it to say, okay,  
11 cytology was negative, but this one is positive. And  
12 you're placing a great deal of weight on the fact that  
13 this is positive when we know that in only 14-1/2  
14 percent of cases will this truly be positive. But  
15 you're going to keep looking and looking and looking,  
16 and I think that there's a risk of morbidity, then, to  
17 the patient.

18 DR. KEMENY: Well, I mean, you know,  
19 everything is within reason. I mean, I don't know if  
20 you would keep looking and looking and looking. And  
21 also, you know, that's why it's important to have a  
22 value at all. I mean, you have to use clinical  
23 expertise. And the more this is on the market, the  
24 more we'll learn what things do mean.

25 I mean, here we just have like 56 people

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1 with cancer. I mean, you know, when this gets on the  
2 market we're going to be talking about hundreds of  
3 people, so we'll know what things mean. But, I mean,  
4 I would imagine that somebody who comes in with a  
5 value of between five and 10 and has all negative  
6 tests probably -- this is probably the way I would do  
7 it, being a surgical oncologist and not a urologist --  
8 I would probably follow that person and make sure that  
9 this test stays in the same range.

10 On the other hand, if a person comes in  
11 with a value of 30, and all of the other tests are  
12 negative, yes, you might keep looking. I mean, the  
13 values are important. But the point is that, at five,  
14 it raises a red flag, and then you do the other stuff  
15 that you're supposed to be doing anyhow. I mean, it's  
16 supposed to be in conjunction with everything else.

17 DR. DiLORETO: This is a positive, I  
18 believe, to clinicians. The long term, the clinical  
19 studies, you know, the outcome studies, the  
20 longitudinal stuff that gets out there in the peer  
21 journals will dictate the specifics of this. This is  
22 significant. This is an additive to what we currently  
23 have to evaluate these patients.

24 I don't believe that there is any safety  
25 issues or major safety issues from the standpoint of

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1 further evaluations. Again, the long term will  
2 dictate how it gets used. It is significantly  
3 additive to the current armamentarium of evaluation of  
4 these particular high risk patient groups. And I  
5 think we'll eliminate the misses, and the misses are  
6 disastrous.

7 DR. LADOULIS: If there is relative  
8 exhaustion at this point --

9 (Laughter.)

10 -- of comments and concerns, it is  
11 appropriate now for us to take a break, following  
12 which we will reconvene for the specific purpose of  
13 making recommendations, any conditions, and take a  
14 vote.

15 We will break for 15 minutes, until 2:40  
16 by that clock over there. Is that reasonable? Okay.

17 We're recessed for 15 minutes.

18 (Whereupon, the proceedings in the  
19 foregoing matter went off the record at  
20 2:26 p.m. and went back on the record at  
21 2:44 p.m.)

22 DR. LADOULIS: Can we reconvene now the  
23 panel for our final session, please? Okay.

24 And as an introduction to this final part  
25 of today's panel, we'll have Louise Magruder, the

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1 Executive Secretary, read some instructions for us.

2 Okay?

3 MS. MAGRUDER: The medical device  
4 amendments to the federal Food, Drug, and Cosmetic  
5 Act, as amended by the Safe Medical Devices Act of  
6 1990, allows the Food and Drug Administration to  
7 obtain a recommendation from an expert advisory panel  
8 on designated medical device premarket approval  
9 applications -- PMAs -- that are filed with the  
10 agency.

11 The PMA must stand on its own merits, and  
12 your recommendation must be supported by safety and  
13 effectiveness data in the application, or by  
14 applicable publicly-available information.

15 Safety is defined in the Act as reasonable  
16 assurance, based on valid scientific evidence, that  
17 the probable benefits to health, under conditions of  
18 intended use, outweigh any probable risks.  
19 Effectiveness is defined as a reasonable assurance  
20 that in a significant portion of the population the  
21 use of a device for its intended uses and conditions  
22 of use will provide clinically significant results.

23 Your recommendation options for the vote  
24 are as follows. The first option is approval, if  
25 there are no conditions attached.

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1           The second option is approvable with  
2 conditions. The panel may recommend that the PMA be  
3 found approvable, subject to specified conditions,  
4 such as physician or patient education, labeling  
5 changes, or a further analysis of existing data.  
6 Prior to voting, all of the conditions should be  
7 discussed by the panel.

8           The third option is not approvable. The  
9 panel may recommend that the PMA is not approvable if  
10 the data do not provide a reasonable assurance that  
11 the device is safe or if a reasonable assurance has  
12 not been given that the device is effective under  
13 conditions of use prescribed, recommended, or  
14 suggested in the proposed 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           At this time, Dr. Ladoulis will be calling  
19 for a motion and will be asking the voting and  
20 temporary voting members of the panel to make a  
21 recommendation on this PMA. For today's panel, voting  
22 members present are Drs. Carpenter, Hortin, Kemeny,  
23 Petrylak, and Taube. Appointed as temporary voting  
24 members for today are Drs. Berry and DiLoreto.

25           DR. LADOULIS: Okay. Thank you, Louise.

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1           At this time, there is a time allowance or  
2 allocation for any of the FDA staff for any subsequent  
3 comment.

4           DR. GUTMAN: FDA has no further comment.

5           DR. LADOULIS: Okay. There being none,  
6 next from the sponsor. Is there any additional  
7 comments you would like to make with regard to this  
8 issue? There being none, then we will proceed to the  
9 issue of voting on this application.

10           I'm going to turn, first, to Dr. DiLoreto,  
11 if you would like to make a proposal for the motion.

12           DR. DiLORETO: I would like to move  
13 approval with conditions, and the condition that I  
14 would like to see changed is the labeling issue, that  
15 the product be used, as previously mentioned, in  
16 conjunction with and not in lieu of current standards  
17 of care and evaluation of the patients at high risk  
18 with micro hematuria.

19           DR. LADOULIS: So the specific condition  
20 is a change in wording of the claim --

21           DR. DiLORETO: In the --

22           DR. LADOULIS: -- to read --

23           DR. DiLORETO: Yes.

24           DR. LADOULIS: -- to read "in conjunction  
25 with" rather than as it reads now.

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1 DR. DiLORETO: As it reads is "as an aid  
2 to," I believe. I would like it to state "in  
3 conjunction with, and not in lieu of."

4 DR. LADOULIS: We want to -- we have a  
5 motion. Do we have a second for this motion? It's  
6 seconded.

7 Now, let's discuss the condition. We have  
8 to have some discussion about this condition. Okay?

9 DR. KEMENY: I think it's important that  
10 it's -- I mean, because one of the things that we're  
11 worrying about here is that it's not a stand-alone  
12 test. But this test is in conjunction with the other  
13 tests that we have. So that's how this test will be  
14 valuable. I mean, that it goes along with cytology,  
15 cystoscopy, upper tract evaluation. This is added to  
16 that. It doesn't -- should not stand alone, and I  
17 think it's important to specify that in the labeling.

18 DR. LADOULIS: Okay. Dr. Petrylak?

19 DR. PETRYLAK: I think the word "aid" is  
20 very vague in this situation. I think that can be  
21 interpreted from the most extreme to be saying that we  
22 will use this to -- in conjunction with our other  
23 standard tests. But also, an individual may interpret  
24 that as saying, "Well, fine. I've got a negative  
25 test. I don't want to go further with the workup."

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1           And I think that if we specify that it be  
2 done in conjunction with other standard tests that it  
3 would be a clearer indication for the product.

4           DR. LADOULIS: Do you want to specify that  
5 specific tests -- any -- okay.

6           DR. KEMENY: We think it would not be a  
7 good idea to specify --

8           DR. LADOULIS: All right.

9           DR. KEMENY: -- the tests because it may  
10 be that those tests would change. So that's why we'd  
11 like to say the current standards.

12           DR. LADOULIS: Okay. Are there any other  
13 comments or discussion about this amendment to the  
14 motion -- this condition?

15           DR. BERRY: I'm not clear on whether it  
16 addresses the issue of cutoff at all.

17           DR. LADOULIS: This is not addressing  
18 that. We can come to that issue separately.

19           DR. BERRY: Okay.

20           DR. LADOULIS: This is just in regard to a  
21 discussion of one amendment condition, and that has to  
22 do that the -- a labeling claim specified that it is  
23 to be used in conjunction with standard procedures for  
24 the diagnosis of urinary tract cancer, correct?

25           Any other questions about this specific

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1 amendment? Dr. Taube?

2 DR. TAUBE: Well, I mean, I think the  
3 question that Don was actually raising is whether we  
4 have to then make a separate motion --

5 DR. LADOULIS: Yes.

6 DR. TAUBE: -- to make another condition.

7 DR. LADOULIS: Yes.

8 DR. TAUBE: Okay.

9 DR. LADOULIS: We'll come to that  
10 certainly. So on this condition, is that all  
11 acceptable by the -- we'll vote on this condition that  
12 -- the first condition for approval is that, to  
13 restate Dr. DiLoreto's amendment, that it's to be used  
14 in conjunction with other standard diagnostic  
15 procedures, correct?

16 DR. DiLORETO: The specifics of the  
17 verbiage could be --

18 DR. LADOULIS: Could be worked out.

19 DR. DiLORETO: -- changed. But the intent  
20 is in conjunction with, and not in lieu of --

21 DR. LADOULIS: All right.

22 DR. DiLORETO: -- current standards.

23 DR. LADOULIS: All in favor of that  
24 amendment to the condition? All opposed? That  
25 condition carries. Thank you.

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1           Next? Dr. Kemeny, do you have any other  
2 recommendations you want to make?

3           DR. KEMENY: No.

4           DR. LADOULIS: Okay. Dr. Petrylak?

5           DR. PETRYLAK: No.

6           DR. LADOULIS: Okay. Dr. Carpenter? Dr.  
7 Berry, you would like to make a comment?

8           DR. BERRY: I would like to see the cutoff  
9 be 10 instead of five.

10          DR. LADOULIS: Okay. So the specific  
11 condition that you'd like to recommend, is there a  
12 second to that? There is a second to that motion --  
13 that the condition be applied that the cutoff value be  
14 10 units per ml rather than 5.0. Any discussion about  
15 that motion?

16          DR. KEMENY: Nothing that we haven't said  
17 before. But I personally do not think that's a good  
18 idea. I think it should stay at five, as the company  
19 has recommended it, because it -- at 10, it's not as  
20 useful as a diagnostic tool as it is at five, because  
21 of the specificity.

22          DR. DiLORETO: I would concur with that.

23          DR. PETRYLAK: I would also concur with  
24 that.

25          DR. BERRY: Since Dr. Kemeny said that

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1 she's -- nothing that she hasn't said before, I'll say  
2 nothing that I haven't said before. The test has no  
3 value, period, between five and 10.

4 DR. TAUBE: But I would like to add the  
5 comment that because the lowest calibrator is at  
6 7-1/2, I think we have very little confidence in  
7 values that are measured around five. And so the  
8 question is: can they provide a calibrator that's in  
9 a lower range, so that the curve is more precise or  
10 accurate? I'm not sure --

11 DR. LADOULIS: Reproducible.

12 DR. TAUBE: Reproducible. Well, no, I  
13 don't think it makes it more reproducible. I think it  
14 makes it more reliable in that range. Or should we  
15 take the compromise that Dr. Berry suggested before,  
16 which is to have the cutoff at seven, where you have  
17 -- which is in the range, the measurable range?

18 DR. LADOULIS: Dr. Hortin?

19 DR. HORTIN: I don't know. Maybe they  
20 could respond to this. I think that all of the data  
21 that they provided most likely was probably within  
22 kids of probably one to three months of production  
23 under optimal conditions.

24 And if we have this test go out into the  
25 more real-world setting, we're likely to see that the

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1 performance reflected in this evaluation probably  
2 represents better than average. It might represent --  
3 it's hard to know whether it will be substantially  
4 better or not. But, if anything, the performance in  
5 the real-world setting will probably deteriorate.

6 And also, we weren't asked specifically to  
7 comment in terms of the time stability. There was  
8 some information requesting extension of stability of  
9 products from 18 to 24 months. They provided the data  
10 in here. We didn't have any specific request on that.

11 If the cutoff -- particularly if the cutoff is at  
12 five, I would recommend not extending the dating to 24  
13 months.

14 It shows not major -- the test was not  
15 performing terribly at 24 months, but they showed a  
16 substantial reduction in the signal values of about 20  
17 to 30 percent, which would probably be expected to  
18 translate into worsening of the precision by 20 or 30  
19 percent at low levels.

20 So I'm personally in favor of raising the  
21 cutoff level to 10, but I think we might want to look  
22 -- if that doesn't pass, I would suggest another  
23 motion that if the cutoff level happens to be five,  
24 that their should be very serious looking about  
25 whether the dating should be extended or they should

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1 provide additional data in terms of how the precision  
2 and performance is going to be at 24 months.

3 I would expect it to perform significantly  
4 worse than the data that they presented to us here,  
5 and that's kind of another factor in terms of the  
6 comments that I've made before.

7 I guess what we see reflected here is a  
8 little bit of the dichotomy between the clinician's  
9 value when every time something new comes along, they  
10 think that it will somehow get them an advantage. And  
11 then they call up the laboratory people and say,  
12 "Well, you got this number. What does it mean? Can  
13 you run it again?"

14 Or there seems to be generated almost more  
15 confusion than a useful clinical value, and I think I  
16 see kind of a division here between myself, kind of  
17 representing more of a laboratory person or people who  
18 are statistically oriented, and the people who are the  
19 clinicians. And they certainly want to have the best  
20 possible tools to manage their patients. But what is  
21 happening here is that we have kind of a substandard  
22 product for this evaluation, which it is somewhat  
23 better than what we've had before.

24 Approving these cutoffs will discourage  
25 the company from further improvements and kind of

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1 coming up with a product that should perform the way  
2 it should. They made a bad decision going ahead  
3 probably with this product, rather than optimizing  
4 their assay and making one that would perform the  
5 best, to provide the best patient care and the best  
6 clinical decisionmaking.

7 And that was probably an unfortunate --  
8 well, they don't always know exactly what the cutoff  
9 values are going to turn out to be. It might have  
10 anticipated that would be more six to 10 range when  
11 they started, but I think that that is unfortunate. I  
12 guess the -- I think the proposal to have a cutoff of  
13 10 is kind of a response to try to get around with  
14 some of the problems that arise from that.

15 DR. LADOULIS: Dr. Ammirati?

16 DR. AMMIRATI: Maybe I can join you, Glen.

17 I consider myself a laboratory person, and don't see  
18 it that way. First of all, this test has been  
19 available since the '94/'95 timeframe, so the company  
20 has had ample time to look at real-time dating, not  
21 just accelerated, which is sometimes the only thing we  
22 can go to market with in the short term.

23 So I believe your opinion that these were  
24 new kits is not founded on anything because these are  
25 kits that they just could have taken out of inventory.

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1 I don't know either. But the fact that the kit was  
2 available perhaps speaks differently of that.

3 And I think we spend a lot of time always  
4 talking about cutoffs because that's what we have. I  
5 don't believe the data show that there are that many  
6 people between five and 10, that the median for people  
7 who do not have disease is around three, and that  
8 people who have disease in various stages are above  
9 that.

10 I think in clinical practice, if you get  
11 something between five and 10, if you do ask for a  
12 second sample, and that's realistic -- that's not a --  
13 I think an inappropriate thing to do. And when the  
14 test is -- I mean, certainly, I've gone to the doctor,  
15 I've had tests that were borderline, and I've had a  
16 second sample. And I don't think I'm unique, and  
17 that's just sort of the nature of the beast of  
18 laboratory medicine.

19 DR. DiLORETO: It's no different than  
20 repeating the cytology, which gets done every day.

21 DR. LADOULIS: Dr. Berry?

22 DR. BERRY: We've not had data presented  
23 on what happens with a five to 10 if you repeat the  
24 test.

25 DR. KEMENY: But, again, we're talking

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1 about clinical scenarios. I mean, we're looking at --  
2 first of all, we're looking at a group of people that  
3 were 56 -- I mean, I don't know how -- if this is  
4 broken down, but, I mean, there were 56 people with  
5 transitional cell carcinoma. Does anyone know the  
6 number of how many of those were between five to 10?

7 DR. DOMURAD: Yes. 10.

8 DR. KEMENY: 10. There were 10. So --  
9 were there 10 patients?

10 DR. DOMURAD: Yes.

11 DR. KEMENY: I mean, so it's -- there's  
12 not a lot of data. I mean, this is -- they did a big  
13 study. There's only 56 people with bladder cancer in  
14 the study, even though it was -- we're talking about  
15 300 people or more at the beginning. So, I mean, and  
16 then we're basing everything about the five to 10 on  
17 10 people.

18 DR. BERRY: No, 140.

19 DR. KEMENY: No, but only 10 people had --

20 DR. BERRY: That's the whole point. Only  
21 10 out of 140, which is about seven percent.

22 DR. KEMENY: Okay.

23 DR. HORTIN: Well, let me raise another  
24 question. I mean, part of the issue --

25 DR. LADOULIS: We'll need to confine

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1 ourselves to this question and then --

2 DR. HORTIN: Well, the cutoff -- I mean,  
3 if you -- if you perform kind of straight cystoscopy  
4 on an extra 10 percent of people, would you consider  
5 that a totally benign outcome?

6 DR. KEMENY: But these people are going to  
7 get cystoscopy anyhow.

8 DR. DiLORETO: It's not an extra 10; 100  
9 percent of the population is going to get the  
10 cystoscopy.

11 DR. HORTIN: I mean, they're going to  
12 get --

13 DR. KEMENY: They're not getting it  
14 because of the test.

15 DR. DiLORETO: They're not getting the  
16 cystoscopy because of the test. They're getting the  
17 cystoscopy because they have micro hematuria. You're  
18 not doing it more on that extra 10 patients.

19 DR. HORTIN: But you had commented earlier  
20 that instead of doing a flexible --

21 DR. DiLORETO: No. My comment was down  
22 the road, as best practices get developed in looking  
23 at how to evaluate these patients with not just this  
24 test, other things that are available and maybe going  
25 to be available, that we may be able to come up with a

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1 better best practice to evaluate patients with micro  
2 hematuria.

3           Everybody that is presented in this  
4 subject group, and basically every patient that  
5 presents with micro hematuria, gets upper and lower  
6 tract evaluations. My comment was that a percentage  
7 of these patients will have negative cystos, negative  
8 upper tract evaluations, potentially negative  
9 cytologies, if they're done, because some people don't  
10 do them because they don't believe in the cytologies  
11 that are being offered to them from their institution  
12 -- that those end up double negatives. There may be  
13 an index of suspicion because of this test -- to watch  
14 those patients more closely than just saying,  
15 "Negative, they're done, we're not going to do  
16 anything more."

17           It may drive a different clinical practice  
18 down the road, if we get 100,000 patients in the  
19 cohort, or the million or so patients in the U.S. that  
20 currently have micro hematuria, new onset micro  
21 hematuria that get evaluated, that these are going to  
22 be best practices. That's not what we're talking  
23 about today. We're talking about what is -- is this a  
24 good test for what they propose? And the answer is, I  
25 think, yes.

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1 DR. LADOULIS: What we should have --  
2 already have agreed on in the -- at the outset, which  
3 I did not ask you to do, was that this application is  
4 approvable with some conditions. I want to have a  
5 second to that, or somebody motion to -- that it is --  
6 Dr. Petrylak will move this approval with some  
7 conditions.

8 DR. DiLORETO: My original motion was that  
9 with --

10 DR. LADOULIS: Okay. And that's been  
11 seconded. I need to have a vote on that, to affirm  
12 that this is what we are and that the table -- have on  
13 the table now are just the conditions. All those in  
14 favor of approval with conditions for this proposal,  
15 all raise their hands? All opposed? Carried.

16 The recommendation is that this  
17 application is to be approvable with conditions, and  
18 we have settled on one condition already and voted  
19 that -- that has to do with the clinical. Now we're  
20 dealing with condition number two, and that has to do  
21 with the cutoff.

22 And I think everyone has commented about  
23 the cutoff. One of the major concerns -- I'm not a  
24 voting member of this issue, but my concern is that  
25 this assay does not have a control value in or near

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1 the cutoff value, which all immunoassays have to have  
2 at the clinical useful level.

3 And I think that that perhaps is something  
4 that you'd consider in your condition, that the cutoff  
5 be, you know, 10 units until this -- a post-market  
6 approval is done for modification to this test, to  
7 introduce a calibrator in the range of the clinical  
8 threshold, which is to be -- and is proposed -- five  
9 units per ml.

10 I think one of the reasons for the  
11 discordance between the laboratories that was  
12 identified as a concern was attributable to that lack  
13 of calibrators in the region of the threshold.

14 Does anyone want to comment about that?  
15 Is it appropriate, in fact, to have -- maybe, Steve,  
16 could you comment. Is it appropriate to have a post-  
17 market approval condition such as that?

18 DR. GUTMAN: Sure. That's acceptable, to  
19 have a post-market approval condition. It certainly  
20 is a novel idea to use that condition to change the  
21 cutoff, but you are the panel, you get to do it --  
22 recommend what you'd like.

23 DR. LADOULIS: Well, I can -- if you want  
24 to amend your motion that -- if you propose a cutoff  
25 of 10 units until such time as the post-market

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1 approval of a calibrator at the region of threshold,  
2 and the threshold could be at -- approval at --

3 DR. BERRY: Can we do --

4 DR. LADOULIS: -- at five.

5 DR. BERRY: Can we do it one at a time?

6 DR. LADOULIS: Do it one at a time. Any  
7 other comments about the motion that's on the floor  
8 that the cutoff value of this assay be at 10 units per  
9 ml? Any other comments? All those in favor of that  
10 motion? Three. And all of those who are opposed?  
11 Four. So this motion does not carry by three to four.

12 And so that is -- that condition is not an  
13 amendment that's approved.

14 DR. BERRY: Is it legitimate to offer an  
15 amendment that it be seven, the average -- the  
16 weighted average of five and 10, according to the vote  
17 of the committee?

18 DR. LADOULIS: Well, I can --

19 DR. DiLORETO: May I provide a compromise  
20 that we leave it at five, and that a post-marketing  
21 study be looked at to come up with a statistically  
22 significant number, given that it can be done in-house  
23 with the FDA, the what "and is" for that study, and  
24 the length of time.

25 DR. LADOULIS: That may be a

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1 recommendation. Will that be likely to be carried  
2 forward? Is that practical?

3 DR. GUTMAN: Sure. You could establish  
4 five, and we could ask for post-market studies to try  
5 and determine if that holds.

6 DR. LADOULIS: Okay. So do you want to  
7 restate that motion?

8 DR. DiLORETO: That the level be left at  
9 five and a post-marketing study be developed with the  
10 sponsor, in concert with the FDA personnel, to  
11 determine the subject numbers and length of time that  
12 would be required to come up with the statistically  
13 significant level other than five, if there is a level  
14 other than five.

15 DR. LADOULIS: Anybody want to second  
16 that?

17 DR. BERRY: Well, I don't know what I  
18 means.

19 DR. LADOULIS: Okay. Can you make that --  
20 do you want to rephrase that, or do you want to --  
21 someone else want to propose an amendment to that?

22 DR. BERRY: The question, Dr. DiLoreto,  
23 is: what does it mean "a statistically significant  
24 cutoff"?

25 DR. DiLORETO: I'll leave that to the

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1 statisticians --

2 (Laughter.)

3 -- and the panel and the FDA.

4 DR. LADOULIS: I could propose something,  
5 that the lower -- I mean, just a suggestion to move  
6 this along here -- that the cutoff limit be at the  
7 currently available calibrator limit, which is for  
8 this test 7.5 units per ml. That is the lower  
9 calibrated limit which a laboratory can use, and  
10 that's all they have any confidence of using.

11 There is no value below 2.1 which has any  
12 significance, and to measure levels of four and five  
13 is below the level of any calibrator. So for an  
14 enzyme immunoassay, or any immunoassay, the confidence  
15 levels just explode below the threshold.

16 Now, 7.5 may be still a very clinically  
17 useful threshold. But the company is already engaged  
18 in studies -- the NCCLS -- to determine precision and  
19 accuracy of a test at lower levels. And presumably,  
20 there will be other calibrators. So it's reasonable  
21 to assume there will be calibrators below the level of  
22 7.5.

23 If you want to consider such an amendment,  
24 and then propose something like that, I suppose that  
25 can be discussed now.

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1 DR. BERRY: I would like to propose that  
2 amendment, that the cutoff be set at the lowest  
3 calibrated level, which is 7.5, until such time as the  
4 company comes forward with a lower calibration.

5 DR. LADOULIS: Any second to that  
6 amendment?

7 DR. TAUBE: Yes.

8 DR. LADOULIS: Dr. Taube.

9 DR. TAUBE: I second the amendment.

10 DR. LADOULIS: Any discussion about that?

11 DR. DiLORETO: What is the current -- I'm  
12 asking the sponsors, what is the current status of  
13 calibration units below 7.5?

14 DR. DOMURAD: The lowest calibrator is at  
15 about 7.5 right now.

16 DR. BRIGGMAN: Hello. I'm Dr. Joe  
17 Briggman. I'm Director of R&D at Matritech. All of  
18 these calibrators in manufacturing have specification  
19 ranges, target ranges for them to hit. And the 7.5 is  
20 with the current kits that were used for this. The  
21 calibrator -- that lowest calibrator can be set in --  
22 I'm not exactly sure what the optimum range is, but a  
23 specification range -- but it's one or two units per  
24 ml down there already.

25 So what can be done without really any

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1 change in our SOPs and manufacturing formula is make  
2 sure that our calibrator is set at the lowest end of  
3 that specification range. And that could put that as  
4 low as a five, or it could be around a six. So --

5 DR. LADOULIS: Well, that's for --

6 DR. BRIGGMAN: I just wanted to bring the  
7 point up that calibrator two is not fixed at seven --

8 DR. LADOULIS: But that's based on just  
9 what's currently available. That's --

10 DR. KEMENY: I'm sorry, but I'm confused  
11 about this. What does it mean that the lowest  
12 calibration level is 7.5? What does that mean?

13 DR. LADOULIS: That there's no confidence  
14 in a value of five and four.

15 DR. KEMENY: Is that correct?

16 DR. LADOULIS: Because you have --

17 DR. BRIGGMAN: Personally, I don't agree  
18 with that. But there is a train of thought that  
19 that's the lowest value that has an absolute value --  
20 a reference value -- upon which other measurements are  
21 made. However, when you're using a standard curve,  
22 not all of -- the calculated value is not solely  
23 dependent on that single calibrator.

24 DR. LADOULIS: There still can be  
25 conditions of post-market, you know, approval

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1 conditions that can change this, if you wish. But --  
2 Dr. Ammirati?

3 DR. AMMIRATI: I don't know if this is  
4 helping or not. But if -- for the lowest calibrator  
5 of seven, 7.5, that says between zero and 7.5 you've  
6 got this part of your curve, which you've sort of  
7 anchored.

8 And so points between zero and 7.5 rely on  
9 this absorbance, which is -- usually gets measured,  
10 and then there's other calibrators, so you get as  
11 close as you can, if it is a linear regression  
12 agreement that goes through zero and infinity as a  
13 straight line, like we saw in some of the linear  
14 regression graphs.

15 Now, the lowest limit of detection is two.  
16 I saw their lowest control is about seven, so that's  
17 somewhat close to the lowest calibrator. I think we  
18 might be doing too much fine tuning. But in  
19 conventional laboratory medicine, certainly you have  
20 most -- more -- the most amount of confidence in  
21 values that are somewhat by your lowest and highest  
22 calibrator, because that brackets the assay.

23 I don't know if that's helpful or not, but  
24 it's another way of looking at it.

25 DR. LADOULIS: Want to restate the motion?

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1 DR. BERRY: That the cutoff be 7.5, the  
2 current lowest calibrated value that was used in the  
3 studies that we've been presented, until such time as  
4 the control -- as the calibration is lowered to some  
5 other point.

6 DR. LADOULIS: Is that what you  
7 understand? That's what you seconded? Any other  
8 comments about this? Any vote on this? Anybody want  
9 to make any other comments? Otherwise, we'll vote on  
10 this amendment.

11 All those in favor of this amendment of a  
12 threshold of 7.5? Five. Okay. Opposed? All right.  
13 That motion carries. That condition is the  
14 recommendation to the agency.

15 Any other conditions? We have two  
16 conditions now that have been proposed that -- the  
17 clinical indication for use, labeling. The second has  
18 to do with the cutoff. Are there any other conditions  
19 that any of the panel want to propose?

20 There being none, we come back now to the  
21 approval of this motion with the two conditions, as  
22 they have been stipulated. Number one, that the  
23 labeling include the wording "in conjunction with the  
24 standard procedures for the diagnosis of urinary tract  
25 cancer." And condition number two, that the standard

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1 cutoff be 7.5 units per ml, pending the --

2 DR. BERRY: It may be a semantic thing,  
3 but I very much like Dr. DiLoreto's followon to the  
4 "in conjunction with, and no in lieu of." So I would  
5 like to see that actually carried in --

6 DR. LADOULIS: I think that stipulation is  
7 in there.

8 DR. BERRY: Okay.

9 DR. LADOULIS: "In conjunction with," and  
10 that wording, in fact, for --

11 DR. BERRY: "And not in lieu of."

12 DR. LADOULIS: Right.

13 DR. BERRY: Use actually those words.

14 DR. LADOULIS: Yes. That's very specific,  
15 as I understand, from Dr. DiLoreto. That is on the  
16 record. That condition is in conjunction with and not  
17 -- that no other recommendation is made.

18 All right. And the second condition is  
19 that the 7.5 units per ml cutoff, until such time as  
20 the post-market approval of a sponsor has provided  
21 evidence to the agency that they have sufficient  
22 standards to warrant --

23 DR. KEMENY: No.

24 DR. LADOULIS: No?

25 DR. KEMENY: No. That they have -- until

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1 they have a calibrator.

2 DR. LADOULIS: Until they have a  
3 calibrator.

4 DR. KEMENY: That is five.

5 DR. LADOULIS: Yes, at five units per --

6 DR. KEMENY: That was what we voted on.

7 DR. LADOULIS: That's right. 7.5 until  
8 the sponsor has provided -- has a calibrator in the  
9 region of five units per ml.

10 DR. KEMENY: And then they can do it with  
11 five.

12 DR. LADOULIS: Then they can submit it to  
13 the agency, and the agency can reach agreement. So  
14 that is the motion that's on the floor.

15 DR. DiLORETO: So moved.

16 DR. LADOULIS: Second?

17 DR. PETRYLAK: Second.

18 DR. LADOULIS: Any other comments about  
19 the motion? All those who are in favor of? All  
20 opposed? That motion is carried, and so that  
21 concludes the voting on this application.

22 Then, I'll turn the session back to our  
23 esteemed Executive Secretary.

24 MS. MAGRUDER: On behalf of the Center for  
25 Devices and Radiological Health, I want to thank this

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1 panel for their participation in the Center's  
2 activities. I want to congratulate the sponsor,  
3 Matritech, on their well prepared presentation. And I  
4 want to thank all of the FDA staff for their thorough  
5 and effective presentations.

6 I especially want to thank Joan McLean  
7 Bennett for her invaluable assistance during the  
8 preparation for this meeting, and my heartfelt thanks  
9 to the Integrity Committee and conference management  
10 staff for their intensive labor in preparing for this  
11 panel meeting.

12 DR. LADOULIS: Thank you. We are  
13 adjourned.

14 Thank you, ladies and gentlemen.

15 (Whereupon, at 3:20 p.m., the proceedings  
16 in the foregoing matter were adjourned.)  
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