

UNITED STATES OF AMERICA
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

+ + + + +

RADIOLOGICAL DEVICES PANEL

+ + + + +

MEETING

+ + + + +

MONDAY,

MARCH 5, 2001

+ + + + +

5548 01 MAR 21 P4:43

This transcript has not
been edited and FDA
makes no representation
regarding its accuracy

The panel met in Room 020B, Center for
Devices and Radiological Health,, 9200 Corporate
Boulevard, Rockville, Maryland, at 9:00 a.m., Brian S.
Garra, M.D., Chairman, presiding.

PRESENT:

BRIAN S. GARRA, M.D., Chairman

WENDIE A. BERG, M.D., Ph.D., Voting Member

STEVEN E. HARMS, M.D., Voting Member

MINESH MEHTA, M.D., Temporary Voting Member

MARILYN R. PETERS, M.N. M.P.H., Non-Voting
Consumer Representative

JOHN J. SMITH, M.D., J.D., Temporary Voting
Member

ALICIA Y. TOLEDANO, Sc.D., Voting Member

ROBERT J. DOYLE, Executive Secretary

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

C-O-N-T-E-N-T-S

	PAGE
Introductions	3
Update on FDA Radiology Activities, Robert A. Phillips	5
Conflict of Interest Statement, Robert J. Doyle	6
Open Public Comment, Jim Clapp	11
P000041 Sponsor Presentation:	
Introduction, Michael H.Y. Yeh, Ph.D.	16
Lung Cancer, Charles White, M.D.	17
CAD in Chest Radiography, Kunio Doi, Ph.D.	23
RapidScreen RS-2000 System, Ed Martello	26
Case Examples and Clinical Trial, Matthew Freedman, M.D.	28
Clinical Study Results and Conclusions, Matthew Freedman, M.D.	32
FDA Presentation:	
PMA Overview, Robert Doyle	44
Clinical Review, William Sacks, M.D., Ph.D.	47
ROC Analysis, Robert F. Wagner, Ph.D.	68
Statistical Analysis, Marina Kondratovich, Ph.D.	82
Summary, William Sacks, Ph.D., M.D.	96
Presentation by Ron Khazan, M.D.	107
Presentation by Alicia Y. Toledano, Sc.D.	112
Panel Discussion	114
Questions to the Panel	160
Panel Recommendations	203

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
 1323 RHODE ISLAND AVE., N.W.
 WASHINGTON, D.C. 20005-3701

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

(9:08 a.m.)

CHAIRMAN GARRA: Good morning, everyone.

I would like to call this meeting of the Radiological Devices Panel to order.

I also want to request everyone in attendance at this meeting to sign in on the attendance sheet that is available at the door.

I note for the record that the voting members present constitute a quorum, as required by 21 CFR, Part 14.

And I'll begin. My name is Brian Garra. I'm Professor of Radiology at University of Vermont, College of Medicine, and I'm the Chairman of this panel.

Alicia, do you want to start next?

DR. TOLEDANO: My name is Alicia Toledano. I'm a biostatistician on the faculty of Brown University. I'm an assistant professor, and I'm a full voting member and also the lead reviewer for this PMA.

MR. SEGERSON: I'm Dave Segerson, representing the FDA. I'm the Acting Director of the Division of Reproductive Abdominal and Radiological Devices.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 MS. PETERS: Marilyn Peters. I work at
2 the West Los Angeles VA Medical Center. I'm the
3 consumer representative for the panel, non-voting
4 member.

5 DR. BERG: Dr. Wendie Berg. I'm Director
6 of Breast Imaging, Associate Professor of Radiology at
7 University of Maryland, and I'm a full voting member.

8 DR. HARMS: I'm Steve Harms. I'm a
9 radiologist, Professor of Radiology, University of
10 Arkansas for Medical Sciences, and I'm a full voting
11 member.

12 DR. MEHTA: I'm Minesh Mehta. I'm a
13 radiation oncologist, Chairman of the Department of
14 Human Oncology at University of Wisconsin. I'm an
15 Associate Professor in Human Oncology.

16 DR. SMITH: And I'm John Smith. I'm an
17 Assistant Professor of Radiology at Massachusetts
18 General Hospital, Harvard Medical School, and I'm a
19 radiologist and a full voting member.

20 MR. DOYLE: And I'm Bob Doyle, the
21 Executive Secretary for this panel.

22 CHAIRMAN GARRA: Thank you.

23 Dr. Robert Phillips, the Chief of the
24 Radiology Branch of the Office of Device Evaluation,
25 would now like to give a brief update on FDA radiology

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 activities.

2 Bob.

3 DR. PHILLIPS: This will be very quick for
4 the benefit of the panel and the audience.

5 Since the last time we met, we have come
6 out with supplements for General Electric's digital
7 mammography. These have been two. One has been a
8 supplement for a replacement printer, our copy device
9 that goes with the system.

10 And more importantly, they have been
11 approved for soft copy use.

12 Well, the other one went away. Okay.

13 The second thing is, and I've handed it to
14 all of you, about two weeks ago we issued a guidance
15 document for digital mammography devices, and for the
16 members of the audience that don't have this, it's
17 located on the center's Web page under "New Items,"
18 and for the panel and also the audience, if there's
19 any comments on the guidance I'd be happy to receive
20 them. Otherwise, thank you very much.

21 CHAIRMAN GARRA: Bob, I have a question on
22 the soft copy for the digital mammo. Was that
23 controversial within the agency or can you give us any
24 further enlightenment on that? Because we discussed
25 it extensively at the panel, and --

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. PHILLIPS: I don't think it was.
2 Pretty much what's in the guidance is the path they
3 followed, and it was acceptable to us.

4 CHAIRMAN GARRA: Thank you.

5 Next I'd like to have Mr. Bob Doyle make
6 some introductory remarks.

7 MR. DOYLE: First I'd like to indicate
8 that two members of the panel were unable to make it
9 because of the weather. They were coming from the
10 West Coast. Mr. Larson, our industry rep., our
11 temporary industry rep. in this case, was stuck in
12 Chicago, and Arnold Malcolm, coming from California,
13 was also unable to make it because of the weather.

14 The following is the conflict of interest
15 statement for this meeting. The following
16 announcement addresses conflicts of interest issues
17 associated with this meeting and is made part of the
18 record to preclude even the appearance of any
19 impropriety.

20 The conflict of interest statutes prohibit
21 special government employees from participating in
22 matters that could affect their or their employees'
23 financial interests. To determine if any conflict
24 existed, the agency reviewed the submitted agenda and
25 all financial interests reported by the committee

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 participants.

2 The agency has determined that no conflict
3 exists. In the event that the discussions involve any
4 other products or firms not already on the agenda for
5 which an FDA participant has a financial interest, the
6 participant should excuse him or herself from such
7 involvement, and the exclusion will be noted for the
8 record.

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

14 In addition, I'd like to read the
15 appointment to temporary voting status.

16 Pursuant to the authority granted under
17 Medical Devices Advisory Committee Charter, dated
18 October 27th, 1990, and as amended August 18th, 1999,
19 I appoint the following individuals as voting members
20 of the Radiological Devices Panel for this meeting on
21 March 5th, 2001: Minesh P. Mehta, M.D. and John J.
22 Smith, M.D., J.D.

23 For the record, these individuals are
24 special government employees and consultants to this
25 panel under the Medical Devices Advisory Committee.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 They have undergone the customary conflict of interest
2 review and have reviewed the material to be considered
3 at this meeting.

4 This is signed by David W. Feigal, the
5 Director for the Center of Devices and Radiological
6 Health.

7 Now, if anyone has anything to discuss
8 concerning these matters which I have just addressed,
9 please advise me now and we can leave the room to
10 discuss them.

11 (No response.)

12 MR. DOYLE: Seeing none, let me indicate
13 that the FDA seeks communication with industry and the
14 clinical community in a number of different ways.

15 First, FDA welcomes and encourages pre-
16 meetings with sponsors prior to all IDE and PMA
17 submissions. This affords the sponsor an opportunity
18 to discuss issues that could impact the review
19 process.

20 Second, FDA communicates through the use
21 of guidance documents. Towards this end, FDA develops
22 two types of guidance documents for manufacturers to
23 follow when submitting a pre-market application. One
24 type is simply a summary of the information that has
25 historically been requested on devices that are well

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 understood in order to determine substantial
2 equivalence.

3 The second type of guidance document is
4 one that develops as we learn about new technology.
5 FDA welcomes and encourages the panel and industry to
6 provide comments concerning our guidance documents.

7 I would also like to remind you that the
8 next two meetings of the Radiological Devices Panel
9 are tentatively scheduled for May 21st and August 13th
10 of this year. You may wish to pencil in these dates
11 on your calendars, but please recognize that these
12 dates are tentative at this time, although I might
13 indicate that that May 21st date is probably a pretty
14 good shot that we will have that meeting.

15 Thank you.

16 CHAIRMAN GARRA: Thank you.

17 Okay. We will now proceed to the first of
18 the two half hour open public hearing sessions for
19 this meeting. The second half hour open public
20 hearing will follow the panel discussion.

21 At these times, public attendees are given
22 an opportunity to address the panel to present data or
23 views relevant to the panel's activities. Three
24 individuals have given advanced notice of wish to
25 address the panel.

1 If there are any others wishing to address
2 the panel, please identify yourselves to Mr. Doyle at
3 this time.

4 (No response.)

5 CHAIRMAN GARRA: Okay. I don't see any
6 additional people asking to speak.

7 I would like to remind the public
8 observers at this meeting that while this portion of
9 the meeting is open to public observation, public
10 attendees may not participate except at the request of
11 the Chairman.

12 I would also ask at this time that the
13 persons addressing the panel come forward to the
14 microphone and speak clearly, as the transcriptionist
15 is dependent on this means for providing accurate
16 transcription of the proceedings of the meetings.

17 If you have a hard copy of your talk,
18 please provide it to the Executive Secretary so that
19 the transcriptionist can use it to help make an
20 accurate record.

21 We are requesting that all persons making
22 statements either during the public hearings or open
23 committee discussion portions of the meetings to
24 disclose if they have a financial interest in any
25 medical device company. Before making your

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 presentation to the panel, in addition to stating your
2 name and affiliation, please state the nature of your
3 financial interest in the organization you represent.

4 Of course, no statement is necessary for
5 employees of the organization.

6 A definition of financial interests in the
7 sponsor company may include compensation for time and
8 services of clinical investigators, their assistants
9 and staff in conducting the study and in appearing at
10 the panel meeting on behalf of the applicant; a direct
11 stake in the product under review, such as one being
12 inventor of the product, a patent holder, owner of
13 shares of stock, et cetera, or an owner or part owner
14 of the company.

15 So we're ready to begin the first open
16 public portion of this meeting. The people that have
17 been asked to speak?

18 MR. DOYLE: Have indicated they would like
19 to speak, yes. These are people who have notified me
20 prior to the meeting.

21 CHAIRMAN GARRA: Are Jim Clapp, Louise
22 McFarland, and Ivan Cepeda.

23 So, Mr. Clapp, if you could come forward.

24 MR. CLAPP: Good morning. My name is Jim
25 Clapp. I'm a four-year lung cancer survivor, and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 that's why I'm here this morning. Thank you for the
2 opportunity.

3 CHAIRMAN GARRA: Okay. No affiliations or
4 anything?

5 MR. CLAPP: Just to play it safe, I was
6 asked to come here by Peggy McCarthy of McCarthy
7 Medical Marketing, and I will be paid an honorarium
8 for coming here.

9 CHAIRMAN GARRA: Okay.

10 MR. CLAPP: I'm not going to take very
11 much time. I simply wanted to try to put a human face
12 on what you all are going to discuss today.

13 I'm standing here today as the result of
14 scientists, people that I consider scientists such as
15 yourselves. My lung cancer was found late. As a
16 result I had my entire left lung removed, and as I
17 say, I am a four-year survivor.

18 Over the past two and a half years, I've
19 been averaging burying people who have had lung cancer
20 once a month, and that's directly related to the fact,
21 I think, that their cancers are being found too late.

22 What you're going to be discussing today,
23 I believe, is something that may be able to find
24 tumors earlier and, in my layman's opinion, any
25 cancer found earlier is easier to treat. The

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 curability is a topic in lung cancer that's kind of
2 been debated a lot. All I know is I'm standing here
3 today in complete remission when I was told I might
4 only have six months to live.

5 And it's not because of me. It's because
6 of advances that you all have been involved with and
7 promote, and all I ask is that you think today of the
8 people that couldn't be here, the literally millions
9 of people who have died of lung cancer because their
10 cancer was found too late.

11 So as you're weighing the scientific
12 parts, please just think of the cost in human terms.
13 I know you probably do that. I'm not trying to be
14 presumptive, but I mean, a lot of people die of this
15 disease, more than the next three cancers combined on
16 an annual basis.

17 And I'm 46. I got it at 42. It's not the
18 stereotype of the disease that it used to be.

19 So I thank you for the opportunity just to
20 speak my mind.

21 Thank you.

22 CHAIRMAN GARRA: Thank you very much.

23 The next speaker is Louise McFarland. Ms.
24 McFarland.

25 MR. DOYLE: I believe she called and left

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 a message that she could not make it, and I'll just
2 add it's not because of the weather, but her
3 radiation. She's had some adverse reaction from her
4 radiation treatment she's undergoing.

5 CHAIRMAN GARRA: Okay. The final speaker
6 is Ivan Cepeda. Mr. Cepeda.

7 MR. DOYLE: I haven't heard anything from
8 him.

9 CHAIRMAN GARRA: Well, that might be
10 weather related.

11 MR. DOYLE: Well, we'll give him an
12 opportunity. If he arrives late, he can speak in the
13 afternoon public session then.

14 CHAIRMAN GARRA: Okay. Well, so we've
15 heard from one speaker. The other two are not here.
16 That concludes the open portion of the meeting.

17 We will now proceed with the open
18 committee discussion portion of the meeting that has
19 been called for consideration of PMA 000041 for a
20 computer aided detection device for identifying
21 regions of interest in chest radiographs.

22 The sponsor, Deus Technologies, will state
23 its case for the PMA and be followed by the FDA
24 presentations.

25 The first speaker will be Dr. Michael Yeh,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 Yeh, the President of Deus Technologies.

2 DR. YEH: Good morning. My name is
3 Michael Yeh. Thank you for giving us an opportunity
4 to introduce our RapidScreen System to the panel.

5 The sequence of this presentation includes
6 Dr. Charlie White will talk about early detection, and
7 Dr. Kunio Doi from Chicago will talk about CAD, and
8 also our staff, Edward Martello is going to talk about
9 our system, and one of our users, Dr. Ron Khazan, is
10 going to talk about his experience.

11 Currently he still cannot make it because
12 of weather and also traffic accident, but we will have
13 maybe Dr. Matthew to present his portion if he cannot
14 make it this morning.

15 That is our system. Our system is used to
16 detect regions suspicious for lung nodules on the
17 chest radiographic, and hopefully that will lead to
18 early lung cancer detection.

19 The indication for use is to identify the
20 regions of interest and which may have features
21 associated with solitary pulmonary nodules, which
22 could represent early stage lung cancer. And the
23 device assists physicians to identify areas which may
24 have been missed.

25 The history of the development, we have

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 spent more than eight years in R&D effort in this CAD
2 device, which has resulted in numerous patents either
3 granted or pending, and we also have collaborated with
4 the universities which are involved in this
5 technology, and also partially supported by NIH, NCI
6 through SBIR Program, and there are numerous
7 publications for this particular organ development.

8 The technologies include 87 proprietary
9 features which are derived from clinical information,
10 and we use multiple resolution analysis approach and
11 also multiple stage classification process, which
12 includes artificial neural network, fuzzy logic, and
13 to make our patent recognition.

14 This is a very unique and diverse training
15 database we have collected during the last more than
16 eight years. We have collected data from actually six
17 countries. There are more than 1,000 chest
18 radiographs containing T1 lung cancers and also 10,000
19 cancer free chest imagines and with a follow-up to
20 assist this development.

21 And I should mention the clinical study
22 image database is independent from our training
23 database.

24 Next I will ask Charlie, Dr. White, to
25 give the next presentation.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. WHITE: Good morning. I'm Charlie
2 White. I am the Director of Thoracic Imaging at
3 University of Maryland, and my role here is as a
4 consultant to Deus Technologies.

5 Do you need further disclosure beyond
6 that? Is that fine?

7 CHAIRMAN GARRA: That should do it.

8 DR. WHITE: Okay. Well, what I'm going to
9 do in the next several minutes really is try to
10 provide a context for lung cancer and early detection,
11 sort of a way of looking at lung cancer as a means to
12 facilitate the discussion that follows.

13 I think the first thing that this chart
14 here demonstrates to particularly effective advantage,
15 and this is actually in men by site, that there's been
16 a rapid increase in the prevalence or the rate of lung
17 cancer over the preceding multiple decades. At this
18 point it exceeds actually many of the next two or
19 three major cancers cumulatively. Lung cancer is
20 higher than all the rest.

21 So it's a very severe problem among men,
22 and then if we go to the next slide, what's also I
23 think less perhaps recognized, certainly when I was a
24 medical student and we were talking about breast
25 cancer as being the leading cause of mortality in

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 women, but now what's happened in the last ten to 15
2 years is that lung cancer has actually exceeded breast
3 cancer and, for that matter, every other cancer in
4 terms of mortality from cancer.

5 And you can see that the tangent of this
6 curve really has not leveled off at this point. So
7 it's quite possible and likely perhaps that we'll see
8 this rate increase further.

9 So this underscores the degree to which
10 lung cancer is a problem, really the leading problem
11 of all types of cancer.

12 Let's move on to the next slide there.

13 Well, what about early detection? The
14 fact of the matter is that the vast majority of lung
15 cancers, as was seen a moment ago, are detected at a
16 late stage. In fact, only 15 percent of lung cancers
17 are detected early on in sort of the Stage 1, which is
18 obviously the best or the most curable stage. The
19 effective treatment is really going to be in the early
20 stage of lung cancer.

21 In fact, because of the bias towards the
22 late occurrence of or late detection of lung cancer,
23 the five-year survival rate for lung cancer is only 14
24 percent, which is an abysmal rate.

25 However, if lung cancer is detected in an

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 early stage, in a Stage 1, the earliest of the four
2 stages, the picture is entirely different such that
3 three in four, at least in the Japanese experience,
4 nine in ten patients survive five years, which is
5 actually a remarkably better statistic.

6 If you look at this, the detection of an
7 additional one percent of early stage lung cancer
8 would save approximately 1,000 patients per year in
9 the United States in 2001.

10 Next.

11 Now, these are some results from this is
12 actually the Mayo lung project, which is one of the
13 major screening trials that was undertaken over 20
14 years ago now, looking at the effects of intervention
15 versus what was called usual care.

16 Intervention meant getting a screening
17 exam, and usual care meant essentially doing what was
18 kind of the convention treatment or the convention
19 intervention at that time. This is obviously more
20 interventional.

21 And you can see that there's clearly a
22 survival advantage both at five years and at multiple
23 years beyond that. If you take it out to even 20
24 years, there's a survival advantage.

25 Now, one of the big controversies --

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 clearly there's a survival advantage. One of the
2 controversies that hasn't been settled, and I don't
3 mean to slip it under the rug, is the issue of
4 mortality, and that's a very controversial topic. But
5 there is a survival advantage, and so there's at least
6 some basis for thinking that screening may have some
7 utility.

8 Clearly, late stage -- these are all early
9 stage -- late stage has an abysmal prognosis no matter
10 whether there's intervention or not.

11 Go on to the next one.

12 The other point that can be made here,
13 just again by way of quick discussion is that the size
14 of the tumor -- these are all the early stage type
15 tumors, the T1 tumors, the less than three
16 centimeters. Really here these are less than two.

17 So if you look at three millimeters to ten
18 millimeters versus 11 to 20, and these are three
19 separate studies, you can see that the survival rate
20 isn't, at least according to these three studies, not
21 influenced by the size of the tumor when you're in the
22 zero to two cm range.

23 And this makes the argument that whether
24 you're using -- this really puts it in the chest
25 radiography size. Certainly when you're above one

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 centimeter, you have the potential to detect lesions
2 on chest radiograph. In fact, you can even go
3 somewhat lower.

4 So as long as you're below two
5 centimeters, it would appear that it doesn't really
6 matter whether you get all that much smaller.

7 Now, again, there are some methodologic
8 issues, but nevertheless, this at least gives the
9 indication that chest radiography has a potential role
10 to play in looking at early detection.

11 Go on to the next one, please.

12 Now, one of the big issues that has come
13 up in probably the past two or three years is the
14 concept of low dose CT and the idea that perhaps low
15 dose CT will allow screening to be successful.

16 The fact of the matter is it may prove to
17 be the case, but to this point it hasn't. Really the
18 early data from low dose CT studies, CAT scan studies,
19 they're really all one-arm studies. They're
20 prevalence and now incidence studies, but there has
21 not been an effective control group.

22 So we really don't know whether CT will
23 prove to be a useful screen test. It has, however,
24 generated a lot of publicity. So one of the things
25 here is maybe to take a step back and say, "Well, CT

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 may or may not work, but let's actually compare it
2 with chest X-ray and sort of go back."

3 And when you do that, you realize, first
4 of all, the dose radiation from chest X-ray is
5 substantially less than that from CT. So perhaps the
6 technique bears further look from that perspective.

7 And the affordability, clearly, is in
8 favor of chest X-ray in the sense that you're looking
9 at \$60 or perhaps less versus on the order of \$300 for
10 low dose CAT scanning, and obviously the high
11 accessibility of the chest radiographic system to the
12 general public.

13 There are a lot more chest radiographic
14 units out there than there are CT scanners, although
15 CT scan has made some inroads. Still, this is by far
16 the most prevalent type of system, and this is
17 indicated by the broad usage of chest radiography. It
18 is the single largest number of imaging studies that
19 are done in the study, are chest radiographs, even in
20 the year 2001.

21 So I believe with that we can move on.

22 I wanted to thank you all for your
23 attention, and I will turn the podium over to Dr. Doi
24 at this point.

25 DR. DOI: My name is Kunio Doi. I'm

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 Professor of Radiology at the University of Chicago.
2 I am consultant to Deus Technologies, and also I have
3 stock options from the company.

4 I have been working on the subject of
5 computer aided diagnosis for the last 16 years or so.
6 I'm very happy to be here to give a brief presentation
7 on the basic concept of CAD and some results.

8 Computer aided diagnosis, CAD, may be
9 broadly defined by diagnosis made by a radiologist who
10 takes into account the computer output as a second
11 opinion. This is an important concept.

12 The computer does not dictate. The final
13 decision is made by radiologist or physician.

14 Why is CAD needed? This is because
15 radiologic diagnosis is made based on subjective
16 judgment. Therefore, radiologics occasionally miss
17 lesions. And also, the variation in diagnosis may be
18 large.

19 Therefore, the purpose of the CAD is to
20 achieve improvements in the quality and the
21 productivity of radiologic diagnosis, specifically to
22 improve diagnostic accuracy and consistency, and in
23 the long run, when radiologists become familiar with
24 the CAD and also when the performance would be
25 improved, I believe that the reduction in time for

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 image reading can be accomplished.

2 There are two general approaches to CAD.
3 One is to find the location of lesions, such as lung
4 nodules on chest X-rays and micro classifications on
5 mammograms.

6 Another one is to quantify the features of
7 normal and abnormal patterns who are benign and
8 malignant patterns.

9 There are three basic technologies
10 required for CAD. One is to do image processing for
11 enhancement and extraction of lesions; secondly, to
12 quantify image features; and, finally, data processing
13 for distinction between normal and abnormal patterns.

14 Now, specifically the purpose of CAD for
15 detection of lung nodules is pointing to suspicious
16 locations of subtle lesions which may be overlooked
17 and also from radiologist's attention to potential
18 lesions as second opinion.

19 This is one of the chest image with very
20 subtle lesion, lung nodules, over partially with the
21 rib. So it is very difficult to detect this lesion.

22 The computer output is shown here with
23 arrowhead showing correctly the location of the lung
24 nodule, and we notice another arrowhead here pointing
25 to a normal anatomic structure, which is called false

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 positive.

2 And it is important to reduce the number
3 of false positives as much as possible in the future.

4 One of the important questions is that
5 when we showed this kind of computer output, could
6 radiologists really use this output for the benefit of
7 their diagnosis?

8 Therefore, we have carried out the
9 observer performance studies using ROC analysis, and
10 this is the results. The ROC curve is improved by use
11 of the computer output, and this was published in 1996
12 in Radiology, and we confirmed the statistical
13 significance in the difference between the Az values
14 of the two conditions.

15 There were 16 radiologists participated in
16 this study. Two are chest radiologists, six general
17 radiologists, and eight residents, and we confirmed
18 that all of the radiologists gained their performance
19 by use of the CAD.

20 And also we noticed that the gains by
21 radiologists, less experienced observers, were larger
22 than those by experienced radiologists, and when we
23 compare the Az values of those radiologists without
24 CAD, attendings generally provided higher Az values
25 than residents.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 However, if we look at the overall result
2 with the use of CAD, the performance levels of
3 residents became comparable to those by attendings.
4 Therefore, those results indicate that the CAD can
5 improve diagnostic accuracy, as well as consistency.

6 Thank you.

7 The next one is Dr. Freedman -- oh, I'm
8 sorry.

9 MR. MARTELLO: Good morning. I'm Ed
10 Martello, Director of Engineering for Deus
11 Technologies, and I'm going to give you a quick
12 overview of the actual implementation of the device.

13 It consists of a custom enclosure in which
14 the processing computer, some power supply, control
15 components, and as we in engineering call it, some
16 glue pieces to make a complete system. The user
17 obviously sees the film digitizer, which is necessary
18 to take the analog film and make a digital
19 representation of it.

20 The processing computer does its work and
21 gives the output either on a flat panel screen or a
22 printed output.

23 Again, we have the input functions, the
24 processor, imaging processing software, a rather easy
25 user interface, and the two forms of display.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 The input acquisition is done with an off-
2 the-shelf approved digitizer, and these are the
3 characteristics that we use in our system. We do not
4 use it to its limit.

5 The output is displayed, again, on a 15
6 inch flat panel monitor and a paper printout which can
7 be stapled to the radiologists' work orders so that
8 when they go to look at the film, they can first look
9 at the film and then look at our results.

10 It is a low resolution output on purpose
11 to encourage the use of the original film, and there
12 are no image manipulation tools on the system, again,
13 to promote the use of the film.

14 The physician performs an initial
15 interpretation on the chest radiograph, reviews the
16 output generated by our system, and then is asked to
17 reevaluate their original interpretation, if
18 necessary.

19 We seem to have stalled here. I think
20 we'll skip the slide that was causing problems, which
21 showed the sequence of operations.

22 Basically the application itself has a
23 log-in screen and a password ID so that we can keep a
24 log of who's using the system, and it's a very simple
25 user menu where you pick one of four choices to scan

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.neargross.com

1 or to exit, things like that, and basically you just
2 drop the film into the digitizer, select "acquire."
3 It scans the film, processes, puts up an image, and
4 also it's printing the image. And you can either look
5 at the result on the screen or at the printed paper.

6 And these are examples of some nodules
7 that have been detected and some examples of false
8 positives. I believe this one is the cartilage, the
9 vessel, and the rib crossing.

10 Since Dr. Khazan hasn't arrived yet, I
11 believe Dr. Matthew White -- Dr. Matthew Freedman will
12 take over for him.

13 Thank you.

14 DR. FREEDMAN: Thank you.

15 Since my introductory slide appears later,
16 let me just say that I am Clinical Director and an
17 advisory to Deus Technologies and also Associate
18 Professor of Radiology, Georgetown University.

19 Ron Khazan is one of the 15 radiologists
20 who participated in the clinical trial and
21 unfortunately got stuck on the Baltimore Beltway
22 because of an accident there that apparently is quite
23 a major accident.

24 So I will quickly go over what it was that
25 he was going to talk about, and the first thing is

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 that the radiologists who used the system were trained
2 using a written text videotape practiced on several
3 cases that reflected the variety of cases seen in
4 clinical practice and in the trial.

5 There were two reading session, first
6 without the RapidScreen 2000, which we call the
7 independent read, and then a second interpretation
8 which was sequential where the radiologist read the
9 radiograph, then looked at the computer information
10 and could revise the diagnosis if needed.

11 Dr. Khazan wanted to make the point that
12 there is a real problem in finding small, solitary
13 pulmonary nodules on chest radiographs in that the
14 small ones are obviously not too common or are
15 difficult to see, and there are hundreds of things to
16 look for on every chest X-ray.

17 Because scars can be common, some of the
18 smallest cancers may be overlooked.

19 Dr. Khazan then wanted to talk about the
20 increasing role of technology in medicine -- next --
21 and to indicate that with some technologies there's a
22 long learning curve. So that, for example, with MRI
23 of the knee, the first few hundred that you read, you
24 really have a lot to learn.

25 Here you have to learn what the computer

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 is doing, but from your previous experience, you know
2 what a lung cancer looks like, and therefore, the
3 learning curve is not as great to use this technology.

4 So that with this short learning curve,
5 one quickly learns how to use the system and how to
6 accept or reject the information provided by it.

7 I think we can skip this slide. We can
8 skip this slide because it's been covered. We can
9 skip this slide because it's been covered.

10 And importantly, Dr. Khazan
11 enthusiastically feels that this is the right time for
12 computer aided diagnosis of lung cancer and that
13 anticipating further improvement in the algorithms, he
14 feels this will be a very useful device both now and
15 increasingly so in the future. With digital
16 radiography, this will become even more useful.

17 And then he wanted to show four cases from
18 the clinical trial, and this is the first one. This
19 is a case where without computer assistance only two
20 out of 15 radiologists recognized this rather subtle
21 lesion projected behind bone. With the computer
22 assistance four additional radiologists detected this
23 primary lung cancer, and this is a lesion either
24 surrounded by scar or the whole lesion is larger. We
25 weren't quite sure what the limit of the cancer was,

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 but it was in this region, and either it's smaller or
2 it's bigger and somewhat irregular.

3 But originally only three out of 15
4 radiologists detected this. With the computer
5 results, an additional two radiologists detected the
6 cancer.

7 Now, you've got to know all of the
8 radiologists would have seen the output. Not all
9 responded to the fact that this was circled, but two
10 additional ones did see it.

11 Here is a third one. Initially no
12 radiologist detected this cancer. With the
13 RapidScreen, three additional radiologists detected
14 it.

15 And case number four, this cancer here,
16 two out of 15 detected this initially. With
17 RapidScreen, three additional radiologists detected
18 the cancer.

19 The point of showing these cases is these
20 are very subtle, difficult cases. The computer
21 identified them. The radiologist, at least some of
22 them, with the highlighting given by the mark were
23 able then to see the cancers.

24 Now I will introduce myself, which I have
25 done already done, and continue.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 The clinical study for this product, the
2 RapidScreen RS-2000, was performed at Georgetown
3 University at our Research Center, and we had three
4 goals.

5 The first was to demonstrate that
6 RapidScreen could detect lung cancer.

7 The second was that radiologists using the
8 system would detect more cancer cases.

9 And the third to address any safety
10 concerns that may occur.

11 So the first thing we did is we did two
12 different machine tests. The first was a test of
13 reproducibility and the second that I'll present is
14 machine sensitivity.

15 Reproducibility is very important because
16 it means that each machine performs consistently and
17 that different machines perform consistently, and so
18 what we did is that we looked at both the inter and
19 intra machine variability in detection.

20 We used 60 films that had well
21 characterized T1 lung cancers. They were
22 independently scanned and processed ten times by three
23 machines. So it's a total of 1,800 images that were
24 used, and the image test set for this is different
25 than the clinical trial test set.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 We defined reproducibility index as being
2 perfect reproducibility. In other words, 100 percent
3 less one standard deviation, and using that, the intra
4 machine reproducibility was 95 percent, and the inter
5 machine variability was 97 percent.

6 The main variability is due to differences
7 in the digitizer, and this is the result of slight
8 differences in positioning, we think, in the
9 digitizer. If you give digital data to the computer
10 algorithm, the reproducibility is essentially 100
11 percent.

12 The second question that we looked at in
13 terms of the machine is what is its performance in the
14 detection of cancer. So this is machine only.

15 We used biopsy proven T1 primary lung
16 cancer cases that were independent from the training
17 cases that were used. T1 means that the cancer is
18 less than or equal to 30 millimeters, not invading the
19 mediastinum or the chest wall.

20 Deus Technologies did not have the truth
21 data. The cases were randomly intermixed with cancer
22 free cases, and the algorithm was frozen prior to the
23 start of the study.

24 This represents the size distribution of
25 the cases, and the lines indicate these are in

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 millimeters. The lines above indicate the number of
2 cases at each size.

3 On the bottom I've listed some of the
4 sizes of cancers found in preceding screening studies
5 and retrospective studies, and so our mean and median
6 size was 15 millimeters.

7 The Hopkins prospective study had two
8 different criteria that resulted in 25 and 35
9 millimeters as the size. Memorial had 25 millimeters
10 as the average size. Mayo had 24 millimeters as the
11 average size.

12 As I said, our average size was 15
13 millimeters.

14 Both the Memorial and the study by Austin
15 -- excuse me a moment -- showed that the average size
16 of missed cancers, those that could be seen in
17 retrospect, was 15 millimeters.

18 We also included cases that had been
19 previously missed, and this just shows the
20 distribution of size of the actionable priors, cases
21 that had been missed originally by two radiologists,
22 but that our expert panel agreed were actionable.

23 This chart shows the performance of the
24 machine by size. The size is shown in the middle
25 here. The cases above are machine detections. The

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 cases below are machine misses.

2 Overall the system detected 66 percent of
3 all cancer cases and 68 percent of the cases nine to
4 15 millimeters in size. The study radiologists
5 unaided detected 68 percent of the cancer cases, but
6 only 58 percent of cancer cases nine to 15 millimeters
7 in size.

8 The next test we did was the clinical
9 study, and this was to determine whether or not
10 RapidScreen 2000 could increase the detection of
11 cancer by radiologists in a clinical trial.

12 The clinical trial design used 15
13 community-based radiology practitioners of the usual
14 quality, and they had to interpret at least 75 chest
15 radiographs a month, and the American Board of
16 Radiology certified.

17 Our case sample consisted of 80 primary
18 lung cancer cases nine to 27 millimeters in size with
19 a mean size of 15 millimeters, and these were
20 intermixed with 160 cancer free cases from the same
21 smoking population.

22 All cases were screened by quality using
23 published standards. All cancer cases had confirmed
24 histology. The location was confirmed by an expert
25 panel, and all cancer free cases were confirmed by at

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 least two years of cancer free follow-up.

2 We randomized the cases prior to the
3 initial read and then rerandomized them prior to the
4 sequential read. We used the multi-reader, multi-case
5 ROC method of Dorfman, Berbaum and Metz, a method that
6 does not include cancer location.

7 We used a continuous rating scale where
8 one end meant low likelihood of cancer. The other end
9 meant high confidence of the presence of cancer. The
10 separation between the two rating sessions was at
11 least one month. We used both an independent read and
12 a sequential read design.

13 We used one thing or two things as
14 exploratory data, mainly to learn whether or not there
15 was an effect from machine false positives and machine
16 false negatives.

17 So we had the radiologists mark location
18 if cancer was suspected and to recommend a decision
19 for CT or biopsy.

20 The radiologists were trained as
21 previously described with written material. They were
22 told essentially how the system works, how to use it.
23 We were told that there would be false negatives and
24 that they should not change their opinion with a
25 machine false negative.

1 In the ROC study, we had one primary and
2 two secondary hypotheses. The primary hypothesis was
3 that of increased detection of lung cancer, that
4 radiologists using RapidScreen will detect more
5 primary T1 lung cancer on chest radiographs than when
6 they worked without RapidScreen assistance.

7 The second was increased detection of
8 smaller cancers, that the radiologists using
9 RapidScreen would detect more of the smaller T1
10 cancers, that is, nine to 15 millimeters using
11 RapidScreen than without RapidScreen.

12 The second of the secondary hypotheses was
13 that the radiologists using RapidScreen would detect
14 more of the primary lung cancers that originally had
15 been missed prospectively by two radiologists, but
16 could be seen retrospectively by the expert panel once
17 the location of the cancer was known, and that they
18 would do better with the RapidScreen assistance than
19 without it.

20 Here are our results. The first
21 hypothesis is the primary hypothesis, that RapidScreen
22 would result in increased detection of T1 lung cancer.
23 We were doing an ROC study, and the initial
24 independent read and the sequential read without are
25 just about superimposed as the bottom portion of the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 ROC curve.

2 The upper green line represents the effect
3 induced by the availability of RapidScreen
4 information, and this showed an increase in Az values
5 that was highly statistically significant, and if one
6 looks at the operating point known from published data
7 and from our pilot study that radiologist normally
8 function at about a 60 to 70 percent sensitivity level
9 in this study, we see that between the independent
10 without or the sequential without and the sequential
11 with, that there is an increase from 65 percent
12 sensitivity to 74 percent sensitivity.

13 The first of the secondary hypotheses was
14 that we would demonstrate increased detection of
15 primary lung cancers nine to 15 millimeters in
16 diameter. Again, we have the ROC curves which show
17 that clearly with RapidScreen assistance, the area
18 under the ROC curve is greater. This is, again,
19 highly statistically significant improvement.

20 And if we look at the improvement, again,
21 using historic data and pilot study data, we can draw
22 this point of activity of where the radiologist had
23 functioned and can show that it increased from 58
24 percent up to 72 percent detection rate.

25 If we look at the overall improvement

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 based on this type of analysis, we can see that for
2 all cancers the improvement was nine percent. For
3 nine to 15 millimeters, it was 14 percent. For 15 to
4 19 millimeters, it was a seven percent improvement at
5 that specific point going from the radiologist's usual
6 operating point.

7 The second of the secondary hypotheses was
8 that there would be increased detection of primary
9 lung cancers originally missed by the two
10 radiologists. Here there were only 18 cases, and
11 these are cases that if you think originally the
12 detection rate was zero.

13 We can see that the green line represents
14 the improvements seen with computer assistance. As
15 you remember, we were doing two separate comparisons,
16 sequential without and sequential with versus
17 sequential without and independent. One of these two
18 values in the sequential study showed a statistically
19 significant benefit from the use of RapidScreen in
20 these very difficult cases.

21 So what we've shown is that radiologists
22 will use the system in a clinical trial and can detect
23 more cancer cases using the system with the system
24 than without using the system.

25 The main improvement is for lesions nine

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 to 15 millimeters in size with moderate improvement 15
2 to 19 millimeters in size.

3 RapidScreen also increased the number of
4 previously missed cancers that could now be detected.

5 Cost benefit and safety. Safety
6 considerations were mainly based on location
7 information because what we were concerned about in
8 terms of safety was whether or not a machine false
9 negative, i.e., the radiologist saw something; the
10 machine did not detect it; did the radiologist change
11 their opinion to a false negative from a true
12 positive?

13 Even though the radiologists have been
14 told not to do this, we found that five radiologists
15 did do this when actually in the clinical trial.

16 Offsetting this with the machine true
17 positives, ten radiologists improved performance and
18 overall, if you look at the combined results all
19 together, ten radiologists improved performance, four
20 stayed the same, and one had decreased performance
21 with the aid of the computer.

22 The second thing that we were interested
23 in was in mapping the combined change in sensitivity
24 and specificity because we felt that the computer
25 system is very sensitive to abnormalities on the films

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 and was able to detect not only cancers, but in this
2 smoking population, many of the cancer free patients
3 had scars.

4 And so we expected that there would be an
5 increased detection of scars as well as cancer, and so
6 we expected that the call-back rate, or one minus the
7 sensitivity, would change as well as the sensitivity.

8 So what I've done here is I've charted the
9 change in two different things: sensitivity and one
10 minus specificity, or call-back rate. This quadrant,
11 up means percent increase in sensitivity for each
12 radiologist. This means percent increase in call-back
13 rate.

14 And you can see that most of the cases
15 fall in the quadrant where there is both an increase
16 in sensitivity, but a decrease in specificity.
17 Because unlike breast cancer where a detection results
18 in the diagnostic work-up and can result in biopsy,
19 here increased work-up of a person without cancer
20 results in a CT, which is an almost completely benign
21 test, but does cost some money.

22 So our safety concern was mainly related
23 to the effect of false negatives in changing
24 radiologists' opinion, but we realized that if the
25 system is to be effective, that there will be

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 increased costs from work-up of people with benign
2 findings, but findings that could not be determined
3 whether or not they were cancer by the radiologists.

4 So in relation to RapidScreen 2000, we
5 have made four claims, and we think that the data
6 support these claims.

7 The first is that the system alone can
8 detect solitary pulmonary nodules in our clinical
9 trial T1 lung cancer in chest radiographs.

10 The second is that using the system a
11 physician can increase the detection of T1 lung
12 cancers nine to 30 millimeters in size on chest
13 radiographs. This was the size included in our case
14 sample.

15 The subsidiary claim is that a physician
16 can detect more T1 lung cancer nine to 15 millimeters
17 in size with the RapidScreen 2000 than without
18 RapidScreen 2000 aid, and subsidiary claim 2(b), a
19 physician can detect more T1 cancer of 15 to 19
20 millimeters in size with RapidScreen 2000 than without
21 RapidScreen 2000 aid.

22 Our third claim is that radiologists using
23 RapidScreen 2000 can reduce the likelihood of missing
24 T1 lung cancer. We think that each of these claims
25 has been supported by the statistical evidence

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 presented from the clinical trial and the machine
2 trials.

3 I'd like to thank the panel and the Chair
4 of the panel and the Chair of the review, Dr. Garra,
5 Dr. Toledano, and the remainder of the panel for their
6 participation in this, and also to thank Dr. Doyle for
7 all of his work in this effort on our behalf.

8 Thank you.

9 CHAIRMAN GARRA: Thank you.

10 Are there any other presenters from the
11 applicant here yet? None have arrived yet.

12 DR. FREEDMAN: Dr. Khazan is not coming.
13 So there are no more presenters from Deus.

14 CHAIRMAN GARRA: Okay. Hold on. I think
15 what we'll do is we're running well ahead of schedule
16 here. Did the panel have any questions that they'd
17 like to ask the applicant at this point, the vendor?

18 (No response.)

19 CHAIRMAN GARRA: None? I was typing a
20 whole list here.

21 (Laughter.)

22 CHAIRMAN GARRA: Well, at the request of
23 Bob Doyle, I think we'll take a short coffee break and
24 bladder break for everyone. Let's make it ten
25 minutes. I have ten after ten. So we'll be starting

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 in at 20 after.

2 Thank you.

3 (Whereupon, the foregoing matter went off
4 the record at 10:11 a.m. and went back on
5 the record at 10:26 a.m.)

6 CHAIRMAN GARRA: Why don't we all start
7 assembling and get underway again?

8 Okay. I think we're ready to get underway
9 again, and we're going to start with the FDA
10 presentations. The first one is going to be presented
11 by Bob Doyle, and this will be an overview of the PMA.

12 Bob.

13 MR. DOYLE: Good morning, panel and Mr.
14 Chairman.

15 As you no doubt know by now from the
16 sponsor's presentation, that the device we're
17 considering here under PMA 000041 is for the
18 RapidScreen RS-2000, and it's a computer aided
19 detector for the identification of regions of interest
20 on frontal views of plain chest X-rays, and the reason
21 for the device is to improve the detection of solitary
22 pulmonary nodules, ones that could represent lung
23 cancer.

24 And of course, the system brings the
25 regions of interest to the attention of the users

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 after -- and that's an important point -- after the
2 initial reading of the radiographs.

3 The indication for use in the original PMA
4 has been modified with the cooperation of the sponsor
5 so that at this point and subject to maybe some minor
6 changes as a result of this meeting, what we currently
7 have sort of tentative agreement on the following is
8 the indication for use for this device, that the
9 RapidScreen RS-2000 is a computer aided detection
10 system intended to identify regions of interest on
11 digitized frontal chest radiographs that may have
12 features associated with solitary pulmonary nodules
13 from nine to 30 millimeters in size, which could
14 represent early stage lung cancer.

15 The device is intended for use as an aid
16 only after the physician has performed an initial
17 interpretation of the radiograph. Thus, the device
18 assists the physician in identifying areas containing
19 a potential lesion that previously may have been
20 missed.

21 You were shown pictorially, in fact, this
22 information by the sponsor, the fact that the device
23 consists of the following items. There's a charge
24 coupled detector that reads the film and its key
25 characteristics are 150 dots per inch with a 12 bit

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 depth, digitizing depth.

2 There's a bar code reader for reading the
3 bar code on the film and tying those into the correct
4 database.

5 There's a PC. It's a pentium 2000 with a
6 Windows 2000 operating system, which contains the
7 detection algorithm, a software package that actually
8 does the interpretation.

9 And then the last two bullets there are
10 the two types of outputs that are available. There's
11 a laser printer for hard copy and a thin film
12 transistor flat panel color display monitor with 1024
13 by 768 pixel resolution, and the device can provide
14 one or both of those outputs.

15 And finally, the team that worked on this
16 PMA here at the FDA is listed above. As the lead
17 reviewer, I coordinated the review efforts of the PMA,
18 and I examined the hazard analysis and manuals
19 contained in the submission, and I found these to be
20 adequate to support the safety and effectiveness of
21 the device.

22 Joseph Jorgens performed the software
23 review, and he found the information provided as
24 sufficient to meet the software concerns as described
25 in the applicable FDA guidances.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 Xuan Vo reviewed the manufacturing section
2 of the PMA. Deficiencies were found in this section,
3 and they have been reported to the sponsor. A
4 comprehensive response to these deficiencies was
5 received on February 12th from the sponsor, and these
6 have been found acceptable.

7 Rachel Solomon examined the submission for
8 bioresearch monitoring concerns. She found that a
9 bimo audit was not indicated for this submission.

10 Dr. Sacks reviewed the clinical and
11 reproducibility aspects of the submission, and he'll
12 report on these next. He will also present a summary
13 of the highlights of the FDA review at the end of the
14 FDA presentation.

15 Dr. Wagner of the FDA's Office of Science
16 and Technology reviewed the ROC analyses included in
17 this submission, and he will give a report of his
18 findings.

19 And finally, Dr. Kondratovich performed a
20 review of the statistical data included in the PMA,
21 and she will present a summary of her findings.

22 So with that, I'll turn it over to Dr.
23 Sacks.

24 DR. SACKS: I would say good morning, but
25 if I did, I think you wouldn't believe anything else

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 I'm about to say.

2 (Laughter.)

3 DR. SACKS: As we've heard a few times,
4 just to start again, this is a computer aided detector
5 for identification of regions of interest on frontal
6 views, not on lateral views, but just on PA or AP
7 views of plain chest X-rays, not CTs, but plain chest
8 X-rays, to improve the detection of solitary pulmonary
9 nodules that could represent lung cancer.

10 For those of you who like brevity, this
11 says the same thing.

12 (Laughter.)

13 DR. SACKS: As we've heard also, that the
14 purpose of a computer aided detector is that the
15 radiologist should first review the X-ray, then review
16 what the device has to add, and then re-review the X-
17 ray.

18 I'm going to review again something that
19 you've seen some years ago when we evaluated a CAD,
20 computer aided detector, for mammography because CADs
21 for chest X-rays are not the only types. We have
22 actually seen computer aided devices for dental X-
23 rays, for CT, and MRI, and I'm sure there will be
24 other modalities. So there is a general category
25 here.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 To just sharpen up some of the difference
2 here, there are two complete different types. This
3 was implicit in what Dr. Doi told you, but I just want
4 to separate these out a little more cleanly.

5 The left-hand column, which is a computer
6 aided detector as opposed to the right-hand column,
7 which is a computer aided diagnosis device or a
8 discriminator or differentiator -- fortunately there's
9 a lot of words that begin with D -- we are dealing
10 with this device with the left-hand column. It's a
11 computer aided detector. It's not a discriminator.

12 Detectors are used to improve the
13 sensitivity primarily of the reader, whereas a CADx,
14 or computer aided diagnostic device, is mainly used to
15 improve the specificity, that is, to decrease the
16 false positives which, in turn, in practice means
17 decreasing the work-ups of lesions that turn out to be
18 benign. That's my own invention, LTB.

19 The CAD, on the other hand, that we're
20 dealing with today is used to reduce the number of
21 false negatives, that is, the number of missed
22 cancers.

23 Another difference is that a CAD scans the
24 entire image and, indeed, is generally used to scan
25 the entire image for the entire population that's

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 being screened or at least that has gotten a chest X-
2 ray in this case. Whereas a CADx only is used on
3 selected patients that the radiologist or the dentist
4 or whoever it may be asks it to discriminate, and it
5 just scans a portion that the reader will indicate to
6 it and will give something like a probability that
7 this is malignant or not, and that is not what we're
8 dealing with in the case of this device today.

9 It's only one that scans the entire image
10 and then indicates a region of interest that the
11 reader may have not looked at.

12 As such, CAD is used to correct errors of
13 detection, whereas a CADx is used to correct errors of
14 interpretation.

15 Now, all CAD detectors -- that's all I'll
16 be speaking about from here on -- are intended to
17 increase the sensitivity, that is, the true positive
18 fraction, but they almost necessarily at the same time
19 increase the false positive fraction, which reading
20 the other way around because of the peculiarity of the
21 definition of specificity decreases it.

22 I used this diagram to illustrate to
23 myself and anybody else who finds it useful how this
24 works. The left-hand part of the line is used to
25 represent just cancers. The right-hand part is used

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 to represent the non-cancers. The boxes represent
2 those that are called positive, whereas the line that
3 doesn't have a box are those that are negative, and
4 you can see here, therefore, all of the possibilities
5 portrayed in this one diagram, that is, negatives
6 among cancers are false negatives. Negatives among
7 non-cancers are true negatives. Whereas positives
8 among cancers are true positives, and positives among
9 non-cancers are false positives.

10 Without the CAD, you would have something,
11 say, this many true positives and this many false
12 positives, and you can see here sensitivity as
13 illustrated on this is the true positive fraction,
14 namely, the fraction of cancers that is represented by
15 true positives, and in this diagram it's something on
16 the order of 60 percent as I've drawn it.

17 The specificity is actually the percentage
18 of true negatives divided by all non-cancers, but I
19 think false positive fraction, which is the false
20 positives divided by all cancers, is an easier concept
21 for me at least to follow.

22 So without the CAD, whatever the true
23 positive and false positive rates may be, the idea of
24 the CAD is to point out areas, regions of interest
25 that the radiologist should look at.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 Now, most of those perhaps or many of
2 those are ones that the radiologist has already looked
3 at, and as you've heard, if they have thought that
4 that is possibly a cancer, once they learn how to use
5 a CAD detector, they should not be backing off on that
6 if it isn't marked by the computer, but rather should
7 use only those areas that are marked by the computer
8 that they had not seen and make a decision: is it a
9 positive or not?

10 And if they decide that, "Uh-oh, this is
11 something I missed. I'm sure glad I have this device.
12 I'm going to work this up," they are calling it a
13 positive, but they cannot yet know whether it's a true
14 positive or a false positive.

15 So that there will be some increase in
16 true positives, and there will be some increase
17 necessarily in false positives, or almost certainly,
18 and therefore, with CAD it enlarges both wings of this
19 so that there are more positives.

20 Now, lung cancer screening has not been
21 recommended because there's been, for one reason, no
22 effective treatment until recently or more recently
23 once they are detectable on a chest X-ray or detected
24 at least.

25 However, treatment has been improving over

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 the last couple of decades, and this is giving rise to
2 a search for better screening methods.

3 Now, why is it that retrospectively
4 visible lung cancers may be missed on a chest X-ray?
5 That is, why are there false negatives? And this
6 applies similarly to mammography we've seen in the
7 past.

8 There are basically two types of errors:
9 errors of detection, that is, failing to see it at
10 all, and errors of interpretation, that is, seeing it,
11 but misinterpreting it.

12 Hal Kundel at the University of
13 Pennsylvania and co-workers have done a lot of work
14 along these lines trying to see how for chest X-rays
15 these compare in frequency, and he found that about 55
16 percent of misses, false negatives on chest X-ray,
17 were errors of detection, and the other 45 percent
18 were errors of interpretation.

19 When we're dealing with a CAD detector, as
20 we are today, only errors of detection, as I pointed
21 out with that table, are correctable by the device.
22 Errors of interpretation unfortunately will not be
23 affected because even if a region is marked and the
24 radiologist looks at it, it's the radiologist who is
25 still making the interpretation.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 Now, of the 55 percent of errors of
2 detection, Hal found, along with his co-workers, that
3 30 percent were so-called search errors I'll explain
4 in a second. The other 25 percent were recognition
5 errors.

6 What they did is they studied eyeball
7 movements of the radiologists as they scanned chest X-
8 rays and found that 30 percent search errors were
9 those cancers that the eyes of the radiologists never
10 even rested on. Whereas 25 percent were those where
11 the eyes rested on it, but apparently it didn't
12 compute, and the radiologist didn't do anything about
13 it.

14 So that is the breakdown, and we will,
15 therefore, -- CAD does have the potential of
16 correcting roughly half, which was very similar to
17 mammography, roughly half of the false negatives.

18 Now, there were two trials that I'll be
19 talking about. One was the reproducibility of the
20 device alone without a reader involved, and it was
21 just to assess the reproducibility of the image
22 digitization and detection of regions of interest.

23 The other was the clinical trial that
24 we've heard about to assess the changes in the
25 radiologist sensitivity and specificity for the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 detection and discrimination of lung cancers.

2 First, the reproducibility trial. As
3 you've heard, there were three systems that digitized
4 and processed 60 cancer containing chest X-rays ten
5 times each for a total of 1,800 digitization
6 processings.

7 The reproducibility that the company
8 calculated was defined in terms only of the device
9 sensitivity, that is, these were all cancer containing
10 films, and so it was defined in terms of the detection
11 rate for actual cancers, not in terms of the
12 consistency of marking other lesions that the panel
13 should consider in looking at these figures.

14 They found that the mean device
15 sensitivity for the three systems they used was 80
16 percent, and the mean standard deviation of this
17 device sensitivity was about four and a half percent,
18 which gives you a 95 percent confidence interval on
19 the sensitivity, which is 80 plus or minus almost
20 twice 4.5 to get the 95 percent confidence interval,
21 which gives you a range of about 71.2 percent to 88.8
22 percent, or roughly 71 to 89 percent, which is a
23 fairly large spread.

24 Now, these figures were presented to you

1 subtracting it from 100 to give something like 95 and
2 a half percent, and this is I'm looking at that the
3 glass is half empty. That was looking at it half
4 full, so to speak.

5 Now, the clinical trial. There were 15
6 radiologists, as we've heard, and we've all looked at
7 a set, the same set, indeed, of 240 chest X-rays
8 comprised of 80 cancer containing films and 160 non-
9 cancer containing films. As you've heard, these were
10 biopsy proven, and these were proven to not have
11 cancer with at least two years of follow-up cancer
12 free.

13 The radiology expert panel picked out good
14 quality chest X-rays from a 25 year old lung cancer
15 screening trial that was done at Mayo, Memorial, and
16 Hopkins. They took only ones that had two-view chest
17 X-rays, that is, frontal and lateral, and again, only
18 good quality films were used.

19 Now, of the 80 cancers, there were 18 that
20 were missed by two clinical radiologists at the time
21 that those trials were done 25 years ago. A
22 radiologist expert panel today, operating today,
23 retrospectively judged these 18 to be actionable. In
24 other words, they did not use in the trial chest X-
25 rays of people who proved to have cancer on whom even

1 a retrospective view by this expert panel couldn't see
2 the cancer. There would be no point in that.

3 These are called then actionable priors.
4 That's 18 of the 80.

5 The other 62 of the 82 were seen by one or
6 both clinical radiologists. Those missed by one,
7 however, could also be considered priors since in
8 actual clinical practice generally radiologists don't
9 read in pairs. They read individually. There may be
10 a few practices here and there, much as with
11 mammography where double readings are done, but by and
12 large it's a single radiologist.

13 So since some of those 62 cancers were
14 undoubtedly seen by one and others by both, to get an
15 idea of how many of the 62 might have been in each
16 category, the literature suggests that approximately
17 11 of these 62 in terms of percentage may have been
18 seen by only one radiologist.

19 Therefore, you might estimate that instead
20 of 18 priors, there were 18 plus 11 or 29 priors from
21 the point of view of a single reader's missing it, and
22 51 current.

23 The only reason that I raise this
24 incidentally, let me just go back to that to just
25 point out one thing, that one of the things that makes

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE, N.W.
WASHINGTON, D.C. 20005-3701

1 cases difficult with chest X-rays is not only the
2 smallness, the size of the cancer, but chest X-rays
3 are the busiest kind of X-ray that a radiologist can
4 look at, and lung cancers are solitary pulmonary
5 nodules, benign or malignant, can hide in any number
6 of places, behind the heart, behind the aorta,
7 overlapping the calcification in the first ribs,
8 behind rib crossings, behind the vessels, the
9 pulmonary vessels, and so on and so forth, and so that
10 there's a lot of difficulty on chest X-rays, which is
11 one of the things that accounts for the lower
12 sensitivity in the 60s that we've seen in this trial
13 than we are familiar with for mammography, where it's
14 in the 80 range on average.

15 And the other point that makes the
16 sensitivity of chest X-ray reading so much lower is
17 that chest X-rays are not taken for the purpose of
18 somebody looking to see if there's a lung cancer.
19 They're taken for scores of other readings. Does the
20 patient have a pneumonia or do they have an enlarged
21 heart, and so on and so forth? And it's an incidental
22 that radiologists are taught also look at that chest
23 X-ray, look at that lung fields to see if there's a
24 cancer, but that's not the question that generally the
25 clinical who has ordered the chest X-ray is asking the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 radiologist.

2 Whereas with a mammogram, there is no
3 other question. The only reason you take a mammogram
4 is to see is there a breast cancer on that film. So
5 that heightens vigilance and accounts in part for why
6 sensitivity on chest X-rays is lower.

7 Now, there were three trial hypotheses, as
8 we've heard. The primary hypothesis was that the
9 device will improve, and while Matthew said the
10 sensitivity of the 15 radiologists, actually what was
11 tested was whether it would improve the ROC
12 performance, which is a matter of ROC area. It's more
13 than just sensitivity.

14 Of the 15 radiologists for detecting lung
15 cancers on all 80, the primary hypothesis dealt with
16 all 80 of the cancer containing chest X-rays.

17 The secondary hypotheses -- actually they
18 were in the reverse order from what you heard this
19 morning in the PMA, but that's all right. That's the
20 same two -- it's the same proposition applied to just
21 the 18 priors, and the second secondary hypothesis was
22 the same applied to only the smaller cancers. They
23 were broken down into the nine to 15 range, the 15 to
24 19 range, and the 19 to 27 millimeter range, and there
25 were 38 of the 80 cancers were in this small range.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Twenty-five were in the 15 to 19 range, and 17 were in
2 the 20 to 27 range.

3 Now, there were three readings, again, as
4 you've heard: the independent without CAD; then at
5 least one month later the sequential without CAD; and
6 immediately following that for this particular chest
7 X-ray, a sequential with CAD.

8 In other words, the radiologist looked at
9 the films, then pressed the button and looked at the
10 CAD output and immediately re-reviewed. So this is
11 seconds apart. This is at least one month to wipe out
12 recall, and just because it's so difficult to say all
13 of the IWOC, or independent without CAD, et cetera, et
14 cetera, I'm just going to call these the first, the
15 second, and the third readings, which one of the other
16 speakers did as well.

17 But I think it will be easier to follow
18 that. Just bear in mind that the gap in time between
19 the second and third readings was seconds, where
20 between the first and the third reading was at least
21 a month.

22 Now, the training sessions were given to
23 the radiologists twice, once before the first reading
24 and again before the second reading. After all, the
25 purpose of waiting at least a month was to wipe out

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 recall, and the assumption was that you may have also
2 forgotten how to take this or do this trial. So they
3 were, again, trained. Eight practice chest X-rays
4 were used in this training session along with, as
5 you've heard from Matthew, the videotape and the
6 written material and so on.

7 One of the things that you will see when
8 Dr. Kondratovich presents her figures is that as some
9 of the radiologists actually did something they are
10 not supposed to do with a CAD detector, and that is
11 that a number of them decreased their positive rates
12 when they looked at the CAD. In other words, they
13 changed their minds in the opposite direction.

14 CAD detectors are not supposed to do that.
15 I think this may be a matter of training, adequate
16 training and a learning curve for radiologists will
17 tell them just as everybody has heard, when you take
18 an exam, if you review your answers and you find
19 you've made a mistake, don't touch it. The odds are
20 you will change more from right to wrong than from
21 wrong to right, and the same thing applies here.

22 If the device fails to make an area that
23 you think is a cancer, this device isn't perfect, and
24 if it doesn't mark, you should not back off from that.
25 You should continue to say this needs a work-up, and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 yet a number of the radiologists, as you will see,
2 didn't follow that dictum even though they were told
3 that by the company, and so they lost in sensitivity,
4 and some lost both sensitivity and false positives.
5 Both positives were decreased. But that, I think, you
6 can lay to a matter of training.

7 Now, two comparisons were made, as you're
8 heard. The third reading was compared both to the
9 first and to the second. This gap here between the
10 first and the third, again, was at least one month
11 later. The gap between the second and third was just
12 a few seconds later.

13 Now, one of the differences between using
14 this comparison and using this comparison is that when
15 you're read a film a month ago or more and you look at
16 it again, the intra reader variability, that is, your
17 tendency to agree with yourself when you look at the
18 same film a month or more later, is not all that
19 terrific, and there is a certain randomness that you
20 get in the difference between the first reading and
21 the third a month later, making these more
22 uncorrelated.

23 Whereas with the second and the third
24 reading, you've only looked at it a second ago when
25 you turned this on. You can't forget what you saw.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 So that these are much, much less uncorrelated, which
2 is a kind of double negative, but it's an important
3 double negative because it means that, as Dr. Wagner
4 will explain in some detail, that the ability to
5 distinguish between the ROC curve for the second
6 reading and for the third is much more separable. The
7 uncorrelated part doesn't swamp the difference as it
8 can in this kind of case.

9 Now, one other difference is that the
10 readings that are done independently here a month
11 before the radiologist is going to use the CAD, and
12 they know when they're reading these first readings
13 that they're going to be using, is that the readings
14 like that, done like that maybe more closely actually
15 simulate actual clinical practice today. That is, we
16 do not have a CAD in place for chest X-rays today.
17 This device will be the first of its kind, and given
18 that the independent reading may more closely simulate
19 what radiologists do today.

20 However, of course, any readings that
21 anybody does in the course of a trial has a certain
22 bias because it heightens your vigilance just by
23 virtue of the fact that you know you're participating
24 in a trial.

25 Nevertheless, the second reading that is

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 done seconds before you're going to turn on the CAD,
2 one might expect -- and, indeed, the data bore this
3 out -- is even more heightened vigilance and perhaps
4 is even farther from clinical practice today.
5 However, one can argue that if there's a difference
6 here, there should certainly be a difference here, and
7 there will still certainly be a difference between CAD
8 and even lower sensitivity perhaps in the actual
9 clinical setting. So keep that in mind as you deal
10 with both of these comparisons.

11 Now, the radiologists recorded three
12 different things. They recorded their confidence on
13 a zero to 100 percent scale that the chest X-ray
14 contained a cancer.

15 The second thing they did was they were
16 asked in those cases where they did think there might
17 be a cancer to indicate whether or not a CT or biopsy
18 was indicated, and there was a place on the screen for
19 them to check one or the other of those.

20 The third thing they did when they thought
21 there was a cancer was to circle it on the screen and
22 to indicate there by the location of the lesion.

23 I just want to make a point about the way
24 this was done. The radiologists when they first
25 brought up the film, the next film, were presented on

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 the computer screen with a line that was extended from
2 zero to 100. It said at the left end definitely
3 absent and at the right end definitely present,
4 meaning cancer, and the marker was placed by default
5 at the midpoint of the 50 percent point on the line.
6 That's the way the screen came up for each film for
7 the radiologist.

8 The task of the radiologist then was to
9 look at the film and move the marker with the mouse
10 either to the left or to the right.

11 Now, the idea of having a zero to 100
12 percent scale is that suppose you were 20 percent
13 confident that there was a cancer. Well, if you were
14 thinking along those lines, you moved the marker from
15 50 percent down to 20 percent, and then you might say,
16 "I'm going to recommend a CT for this. I'm not that
17 confident that there is one, but it's 20 percent, and
18 I'm going to represent it with a CT."

19 If you're fairly confident, like at 70
20 percent confident it's a cancer, you'll mark it or
21 you're move the marker from 50 percent to 70 percent,
22 and again, you'll indicate CT or biopsy.

23 The problem with the default being at 50
24 percent is it was very interesting. There were very
25 few radiologists who moved it to the left and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealgross.com

1 recommended a CT or biopsy. When that happened, that
2 was a very rare event, and it suggests that what they
3 were thinking, despite the instructions, because the
4 marker was placed at 50 percent to begin with is if I
5 don't think there's a cancer, I'm going to move it to
6 the left, and if I do think there's a cancer I'm going
7 to move it to the right, and furthermore, I'm going to
8 move it a distance that's sort of proportional to how
9 confident I am that there isn't or that there is a
10 cancer.

11 Where this has any effect on the readings,
12 on the results of the analysis it not clear, frankly,
13 but it is two different ways of conceiving of this,
14 and it is, of course, possible to have no marker on
15 the slide to begin with. The default may be that
16 there is no marker. You may be asked to put your
17 mouse at some point on the line, click, and then a
18 marker appears which you can then slide a little bit
19 if you want, but that might be less tending to
20 separate the zero to 50 from the 50 to 100.

21 And, indeed, when we look at the data, we
22 see that all of the cancers were distributed in a
23 bimodal curve, that is, a few way down to the left and
24 most way to the right, whereas the non-cancers were
25 also in a bimodal distribution along that line, most

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 somewhere to the left and a few somewhere to the
2 right. They were not a single distribution displaced
3 as we often see if you have just a single zero to 100
4 line.

5 Again, because ROC analysis deals only
6 with the order in which these come up, it's not clear
7 what effect this has.

8 The endpoints that were looked at were the
9 confidence rating, but confidence ratings ignoring
10 location were used to construct the ROC curves along
11 with their variances.

12 The 50 percent confidence points further
13 were used ignoring location again to determine point
14 estimates of sensitivity and specificity, sometimes
15 with their variances. You'll hear from Drs. Wagner
16 and Kondratovich about that.

17 And also location markings were also used
18 to determine point estimates of sensitivity and
19 specificity. So there were two completely different
20 sets of sensitivity and specificity estimates
21 rendered, one ignoring location, the other location
22 specific, and on this you will hear the details.

23 And let me introduce now Dr. Kondratovich,
24 who will give you or I'm sorry. Dr. Wagner first. I
25 beg your pardon.

1 (Pause in proceedings.)

2 DR. WAGNER: This morning I've been asked
3 to give some comments on the ROC paradigm and the
4 paradigm of the receiver operating characteristic
5 curve; some comments on the concept of the
6 localization ROC, which is not used in this study and
7 perhaps you might wonder why; comments about the
8 multiple reader/multiple case, so-called MRMC, ROC
9 paradigm that has been flourishing in the last five
10 years or so; and then I'll give you the applications
11 to the present submission. What does the multiple
12 reader ROC tell us about the two reading conditions
13 that Dr. Sacks just told you about, and a brief
14 overview of the MRMC ROC analysis.

15 The MRMC acronym is also just frequently
16 abbreviated to say we have done a reader study or a
17 reader ROC study.

18 The ROC paradigm, I think everyone is
19 familiar with the general picture. We have overhead
20 stress syndrome there.

21 (Laughter.)

22 DR. WAGNER: I think you know that it's
23 the map of the two positive fractions versus the false
24 positive fraction as a particular latent variable is
25 varied, and we refer to that variable in this field as

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 the reader mindset. It's the level of the
2 aggressiveness of the reader, and as the
3 aggressiveness goes up, he or she picks up more true
4 positives at the price of more false positives.

5 ROC curves are used for several reasons in
6 medical imaging, especially in medical imaging, and
7 perhaps the one that is not appreciated by people who
8 use this in other fields is the following.

9 In clinical laboratory tests there's often
10 a well defined -- one hopes there is a well defined
11 operating point, but in medical imaging it has been
12 known for several decades that there is not a well
13 defined operating point, that observers move all over
14 their own ROC curve, and in a few minutes we'll talk
15 about the fact that readers with different skills move
16 across different ROC curves.

17 Another reason the ROC curve is used is
18 that when you do an average, when you get the area
19 under the ROC curve, you are implicitly replacing the
20 ROC curve with a single line, and when you do that,
21 you're essentially getting the sensitivity, which is
22 down here hiding, the sensitivity averaged over all
23 specificities.

24 A little bit more subtle, but you can also
25 do the same exercise and show that the area under the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealgross.com

1 ROC curve if you take the area this way is specificity
2 averaged over all sensitivity.

3 And now, it's been a long held doctrine in
4 medical imaging for a long time that if two ROC curves
5 do not cross, then the area under the curves is a
6 very useful and essential and perhaps the most useful
7 and rigorous single number summary measure, and it's
8 for the reasons that I just gave.

9 It's also for the reasons of statistical
10 power because if you had some area here in which you
11 were studying the sensitivity and the specificity, you
12 would not get the benefit -- this is really tricky --
13 you would not get the benefit of averaging over the
14 entire space. That's an important point I'd like to
15 make.

16 We have a lot of safety issues here.

17 (Laughter.)

18 DR. WAGNER: Thank you.

19 So what I was just saying is that one of
20 the great reasons for using area under the ROC curve
21 is if two ROC curves don't cross, that is the most
22 useful summary measure of performance, and it buys you
23 an awful lot because if you were just to operate
24 within some narrow region of sensitivity and
25 specificity, then you would get the statistical power

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 of something that's something like binomial
2 statistics.

3 But if you get to average over this entire
4 ROC curve, this is something like buying you a factor
5 of 2N patients. If you want to get the same precision
6 ROC-wise, area-wise as you get in sensitivity, you can
7 do this with half the number of patients, and so it's
8 a very powerful statistical tool to use, and it is
9 unambiguous if ROC curves don't cross.

10 Now, you are probably asking since you
11 heard Dr. Sacks talk about the correct location was
12 not used in the present study, in the ROC analysis,
13 how come. There is the concept of a localization ROC
14 curve in which the correct location identification is
15 required to get credit for a true positive.

16 If you keep score according to the LROC,
17 localization ROC paradigm, as you would expect, the
18 score card goes down. There are parametric models in
19 fitting software to analyze location specific ROC
20 curves, but the test of validating this statistical
21 procedure is still in progress.

22 And the most important point I'd like to
23 make is that there is no software yet to test the
24 differences between systems, and so this field is
25 still maturing.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 On the other hand, this has not been
2 considered an urgency in this field for a long time,
3 however, since there have been several proofs over the
4 last 30 years that the ROC curve actually can predict,
5 within very not too restrictive assumptions, that the
6 ROC curve can predict where the LROC curve falls.

7 Charles Metz, who is present in the
8 audience, was the author of one of the first papers on
9 this subject, and Richard Swensson, who is in our
10 community -- we've met him many times, Alicia -- have
11 demonstrated that this area, this piece in the
12 upper -- oops, here we go with this other stuff. I'm
13 going to go back to Power Point -- that this piece of
14 the area above the ROC curve and the piece between the
15 two curves are equivalent.

16 Now, if you've never heard this before,
17 this may come as quite a surprise to you. In fact, if
18 you just think of two films and keeping score based on
19 whether you've correctly located the lesion or not,
20 you might think this is absurd.

21 But this is, in fact, averaged over a
22 population, and on the average, you get these two
23 results. The differences are, as I just said, the one
24 at curve not only point-wise, but area-wise is
25 predictable from the other, and these results are

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 completely distribution free. There's just a simple
2 decision model that goes into that derivation.

3 So the field has not considered that an
4 urgency. Now I'm going to try to juggle for a minute
5 here. I guess electronics are better than analog
6 schemes.

7 Now we have to talk about the multiple
8 reader/multiple case ROC paradigm, the so-called
9 reader study. The definition is that every reader
10 reads every case, and here in both modalities, and
11 what you can do then is you can model and correctly
12 account for a lot of components on the ROC accuracy
13 measure.

14 Now, I'm not going to walk you through all
15 of these because it gets a little bit technical, but
16 I would like you to realize just a few high points of
17 this breakdown.

18 The components of variance that you can
19 get from multiple reader ROC analysis, they come in
20 two packages. Dr. Sacks more or less set me up for
21 this. There's the package that the components are
22 correlated across the modalities and the package that
23 are uncorrelated across modalities.

24 And let me tell you why the latter is the
25 most critical one here today. First of all, both of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 these have a case piece. The case piece is
2 intuitively what you might expect. It's related to
3 the range of case difficulty. The reader pieces are
4 related to the range of reader skills. So these are
5 the two general ideas I'd like you to keep in mind.

6 And now what about whether these
7 components are correlated or uncorrelated?

8 Remember it's not so bad that readers have
9 great variability because if they vary in a correlated
10 way across modalities, you can still see the
11 difference between the modalities with great
12 precision. And so reader variability does not hurt
13 you if it's the correlated piece.

14 It's only the uncorrelated piece that cuts
15 into your ability to see the difference between two
16 systems, and so the reason for this overhead then is
17 to tell you about the two kinds of components, case
18 and reader, the correlated part, the uncorrelated
19 part.

20 Now, let's talk about the reading
21 conditions again. Quickly Dr. Sacks has more or less
22 covered all of this. The reading conditions -- this
23 is tricky -- condition one, reading two and three, the
24 independent, the sequential without and the sequential
25 with.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 And the question before many of us over
2 the last few months has been: which is the baseline
3 mode, the independent without or the sequential
4 without?

5 And I've found people in the professional
6 community choosing up sides on this, people saying
7 that the independent corresponds to the current
8 reality and others saying, well, the sequential is
9 just as relevant to current reality, but there's a
10 more statistically meaningful point at stake here.

11 In the sequential mode, you may get a more
12 sensitive probe of the difference, and let me explain
13 that to you. What I've said here is that the error
14 bars might be tighter in the sequential mode, and let
15 me tell you how that can come about.

16 I have an overhead, and you received this
17 in your set of handouts, which you've taken and
18 studied diligently, I'm sure, and I'm not going to
19 read you the overhead. I'm going to do a little
20 schematic dance here to explain what's going on there.

21 When we analyzed the sponsor's reader ROC
22 analysis, we found the following. Well, I'm going to
23 do it this way. We found that the correlated
24 components of -- let us think about the independent
25 reading condition. We found that the correlated

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 components and the uncorrelated components were
2 comparable, but when you went to the sequential
3 reading condition, what would you think happened to
4 the correlated parts sequentially?

5 The correlated components of the variance
6 went up. In a counterbalancing way, the uncorrelated
7 components went down in such a way that overall they
8 added up. So that the total reader variance in both
9 schemes, the sequential or the independent, is about
10 the same, which is to say that this sequential reading
11 scheme does not perturb the total reader variability.

12 But when you go to the sequential scheme,
13 the uncorrelated components go down, and that's what
14 it is that gives you the ability to see with a very
15 sensitive probe the difference between the sequential
16 without and the sequential with.

17 So this is a little tricky, and it's all
18 said there in words, but you see it borne out in all
19 of the analysis, and the methods we used to analyze
20 this were published by our group in Academic Radiology
21 last year.

22 So I hope that little schematic when you
23 refresh your memories -- all those many words there
24 were meant to say what I tried to spell out
25 schematically for you.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 Let's just go to some representative
2 results now. There are a lot of numbers here. I'm
3 just going to call your attention to some highlights
4 of this.

5 What I have here is the ROC areas.
6 There's an arrow. There will always be, and the left
7 of the arrow will be without the computer assist. On
8 the right will be with the computer assist, and I have
9 the two reading conditions, the independent and the
10 sequential.

11 And this lab MRC, that's the multiple
12 reader software available from the University of
13 Chicago over the Web.

14 And we have several categories. All
15 cases, the smallest cancer cases; all cases, the
16 smallest cancer cases. The numbers are identified
17 there.

18 And we see a general trend that in the
19 independent reading condition there is a slightly
20 larger effect. However, the error bars are, in fact,
21 tighter in the sequential reading condition, and let
22 me tell you what I'm doing here.

23 The left-hand edge of the error bars is
24 the left-hand boundary of the one-sided 95 percent
25 confidence interval. So that left-hand number

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 identifies the boundary that we estimate that if you
2 were to do this experiment 100 times, 95 of those
3 times the performance would be equal to or better than
4 the number on the left there.

5 And so in the independent reading
6 condition, this gain is, ROC area-wise, is only 0.016,
7 0.017, but when you go to the sequential reading
8 condition, that number goes up to a 19 or 026.

9 Let me see what else I wanted to say about
10 this. I think they're the major features.

11 These ditto points mean that we've
12 actually cross-validated the lab MRMC results with
13 just simple nested case reader bootstrapping.

14 Now, a lot of information on this slide.
15 I just want to call your attention to a few points.

16 Dr. Sacks just said that one thing you
17 could do is you could use the 50 percent confidence
18 rating as a cutoff, and that's what this slide has
19 used, and again on the left of the arrow is without
20 the computer assist. The right is with the computer
21 assist.

22 And let me just call your attention to the
23 one minus the specificity. That's the false positive
24 rate. All of these intervals in both the independent
25 and the sequential condition, all of these intervals

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 contain zero. In that sense the confidence intervals
2 do contain the possibility that there has been no
3 change in the specificity.

4 However, those are error bars that are
5 actually very large, and so I don't think anyone would
6 be able to say very much about whether the specificity
7 has changed here or not.

8 However, if you keep score of sensitivity,
9 again, in the independent reading condition there is
10 a large effect in the mean, but the left-hand boundary
11 of the 95 percent confidence interval is a small
12 number, but when you got to this sequential reading
13 condition, there's still a big effect in the mean
14 here, and the left-hand margin of the one-sided
15 confidence interval goes up. It goes up to .023 or
16 .033.

17 So there is a suggestion here that there
18 is something going on in sensitivity. There's not
19 enough power to say much about specificity, and this
20 is one reason why the entire RC paradigm was used to
21 begin with, because when you go back to that, you'll
22 see that the error bars are much tighter and bear out
23 the point that if you have the advantage of averaging
24 over the entire ROC curve, you, in fact, get much more
25 statistical power.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.

(202) 234-4433

WASHINGTON, D.C. 20005-3701

www.nealrgross.com

1 Now, there is one more wrinkle I'd like to
2 call your attention to. My colleagues and I have been
3 publishing over the last two years on analyzing
4 variability and the components of variability in ROC
5 analyses, and when we did one of the analyses, it cued
6 us to look at the following information.

7 What I have here is the distribution of
8 ROC area performance for all 15 readers for the
9 smallest cancers after CAD. So before CAD the average
10 performance of these people was there around .8.
11 After CAD, the average performance of these people was
12 about .85, analog schemes.

13 However, all of this really obscures the
14 fact that these tick marks, each one of these is a
15 radiologist. There people are skewed highly to the
16 right, and so half of these readers are performing in
17 the high 80s or the lower 90s with the aid of CAD on
18 the smallest cancers.

19 So even though the shift was five points
20 and we discussed the significance a little while ago,
21 all of that was obscuring the fact, and this may be
22 data dredging, but it's not too serious when you see
23 something like this -- we see the reader performance
24 skewed -- at least suggest that we ask the question
25 whether with no training more of these people could

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealgross.com

1 score up around .9, which is an outstanding scorecard
2 for this task.

3 In summary, I tried to argue that you
4 could consider both the independent and the sequential
5 modes. I've argued that both the sequential and the
6 independent modes show a significant effect in the ROC
7 area, and there was slightly more significance with
8 the sequential mode, and I tried to give you an
9 explanation for that because I forgot to say this, but
10 in my rehearsal I said that this situation where the
11 independent variability was like this, switched this
12 way in the sequential model.

13 This is a statistician's dream because the
14 total variance was conserved and not perturbed by the
15 components that determine your ability to see the
16 difference between systems went down, and that's
17 obviously a frequently used design tool and something
18 that statisticians pray for all the time and, in fact,
19 turned out to be the case here.

20 And finally, I showed you a bimodal or
21 skewed distribution after the computer aid, and I put
22 to your consideration whether there's a suggestion
23 that there's further potential gain here.

24 Thank you very much.

25 DR. KONDRATOVICH: Good morning. I will

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 consider the following statistical issues: primary
2 and secondary hypotheses, results of multiple read and
3 multiple cases ROC analysis, areas under ROC curves,
4 sensitivity and specificity based on 50 percent
5 confidence rate, average and individual for
6 radiologist, and sensitivity and specificity based on
7 correct location, averaged and individual for each
8 radiologist.

9 As you heard, there are three hypotheses.
10 The primary hypothesis, that radiologist using
11 RapidScreen would increase their detection of lung
12 cancer nine, thirty millimeters in size, and two
13 secondary hypotheses. Secondary hypothesis number
14 one, that radiologists would increase their detection
15 of lung cancers that had previously been missed by two
16 screening radiologists prior, and secondary hypothesis
17 number two, that radiologists using RapidScreen would
18 increase their detection of lung cancers nine, fifteen
19 millimeters in size.

20 In this clinical study, there are three
21 reading conditions, independent without computer first
22 reading sequential, without computer second reading
23 and sequential with computer, third reading.

24 The multiple reader, multiple case ROC
25 analysis was used for statistical analysis of the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealgross.com

1 three reading conditions. The area under ROC curve
2 was considered as a measure of diagnostic accuracy.
3 In this type of analysis, only information about
4 confidence rate for each field was used.

5 The information about locations of marks
6 and recommended actions was not used in this type of
7 analysis.

8 Let us consider statistical hypothesis.
9 In order to show efficacy of the RapidScreen, it is
10 necessary to show superiority in the terms of area
11 under the curve. For superiority, the following
12 statistical hypothesis with clinical important
13 difference delta should be considered.

14 Now, hypothesis states that difference in
15 the areas under the curve between the reading with
16 computer and reading without computer less or equal
17 than the clinical important difference delta, and
18 alternative hypothesis states that this difference is
19 more than difference delta.

20 If on the basis of the results from the
21 study the null hypothesis is rejected, then the
22 alternative is true. So we may conclude that the
23 reading with computer is superior to the reading
24 without computer.

25 The null hypothesis is rejected if the

1 lower limit of the one sided 95 percent confidence
2 interval of the difference in the area ROC curve is
3 larger than this difference, clinically meaningful
4 difference delta.

5 The lower limit of one-sided 95 percent
6 confidence interval is the same like the lower limit
7 of the two-sided 90 percent confidence interval.

8 If lower limit of 90 percent confidence
9 interval is bigger, is larger than clinically
10 meaningful difference delta, then it's shown that
11 device is superior.

12 If delta, clinically meaningful difference
13 delta belongs to this interval, it means that we can
14 reject our null hypothesis and superiority has not
15 been shown. Future, further studies could establish
16 the superiority, but this study in hand does not and
17 can be such situation when our upper limit of 90
18 percent confidence interval is lower than clinically
19 meaningful difference delta. In this situation,
20 nonsuperiority is shown.

21 We have set questions that which reading
22 condition is the baseline reading independent without
23 computer or sequential without computer, first reading
24 or second. Both these readings has such interesting
25 characteristics that independent without computer

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 correspond to current practice and gives less bias
2 point estimate of difference.

3 But sequential without computer second
4 reading, even it gives more bias point estimate of
5 difference, but can be more sensitive probe of
6 difference because this reading condition is more
7 correlated with sequential with computer reading.

8 Therefore, we will use both reading
9 condition to make our conclusions about areas under
10 the curves. For example, for primary hypothesis for
11 detection of all cancers, this is the area under the
12 curve for third reading with computer. This is area
13 under the curve for first reading, and this is for
14 second reading.

15 You can see the difference between
16 sequential, second reading, and independent -- excuse
17 me -- third reading and first reading is about 3.6
18 percent, with lower limit of 90 percent confidence
19 interval, 1.6.

20 While difference between sequential with
21 computer and sequential without computer is less, only
22 three percent, but the lower limit of confidence
23 interval is bigger because this method usually can
24 give you less variance of difference.

25 Therefore, it was demonstrated that the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE. N.W.
WASHINGTON, D.C. 20005-3701

1 difference in areas between the reading with computer
2 and reading without computer is not less than 1.9
3 percent.

4 This is the result of the multiple reader,
5 multiple cases ROC studies, area under ROC curve.
6 This column presents the area under ROC curve for
7 reading with computer, this first reading, this second
8 reading. This is the difference in the ROC curve,
9 point estimate. This is the point estimate for
10 difference between third reading and second.

11 And this is the lower limit of 90 percent
12 confidence interval. As you saw before, for
13 comparison with first reading, lower limit is 1.6
14 percent, and in comparison with second reading, the
15 lower limit, 1.9 percent.

16 It means that it was demonstrated
17 improvement, 1.9 percent. This is our primary
18 hypothesis.

19 Consider the partition. (phonetic) of
20 cancer films according to the priors and currents.
21 Priors, there are 18 films priors, and you can see
22 that even the difference is positive, but the
23 variance of difference is relatively big. Therefore,
24 this difference is statistically not significant.

25 But in comparison with second reading was

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 sequential without computer. It was demonstrated that
2 the improvement, more than one percent.

3 For current cancer films, there are 62
4 sample size, and you can see this differences, and
5 improvement was demonstrated, 1.5 percent. This is
6 our secondary hypothesis number one.

7 Consider the partition (phonetic) of
8 cancer film according to the size of lesion, like
9 small cancers, medium and large. You can see the
10 differences point estimate in differences in the areas
11 under the curve, and this is the lower limit of 90
12 percent confidence interval.

13 You can see that for small lesions it was
14 demonstrated improvement not less than 2.6 percent.
15 For medium lesions, not less than half percent. And
16 for large lesions, statistically almost the same. The
17 is the secondary hypothesis number two.

18 The next question, of course, that arise
19 is that whether this improvement in the areas under
20 ROC curve delta are of clinical value, and one of the
21 meaning of the area under the curve is that area under
22 the curve has sensitivity average over all
23 specificities.

24 Now, consider sensitivity and specificity
25 based on 50 percent confidence rate. The film is

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 considered positive by radiologists if the confidence
2 rate of this film is larger than 50 percent.

3 This is the result for primary hypothesis,
4 all cancer cases. You can see that the sensitivity
5 increased if we compare with first reading.
6 Sensitivity increased something like 6.5 percent, and
7 specificity decreased 1.7 percent.

8 And if we compare with second reading
9 sequential without computer, sensitivity increased 5.6
10 percent, and specificity decreased 2.5 percent. A
11 confidence interval, very wide. It means that this
12 point estimation very noisy.

13 In this situation, confidence interval
14 contains zero. If we have a sensitive probe, we can
15 see that there are an increase in sensitivity like 2.3
16 percent. All confidence intervals for specificity
17 contains zero. It means that we cannot reject
18 hypothesis that there are no difference in
19 specificity, but potentially the decrease in
20 specificity can be as much as these numbers.

21 So we can see such directions that
22 sensitivity is usually increased and specificity is
23 decreased.

24 If we would like to compare to reading
25 conditions and if we have such situations that

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 sensitivity and specificity reading with computer is
2 better than sensitivity and specificity of reading
3 conditions without computer, then of course it's very
4 easy to make conclusion obviously that the reading
5 with computer is clearly preferred.

6 But we have situation such direction that
7 usually that sensitivity is better, but specificity is
8 worse. Therefore, it's difficult to make conclusion
9 because in opposite direction.n

10 Sometimes predictive values, positive and
11 negative predictive values can help to make this
12 decision. Why? Because, for example, for the
13 positive predictive value, this is the expression for
14 positive predictive value.

15 You can see that, of course, the value of
16 PPV depends on the prevalence of disease. But we
17 apply both reading conditions with computer and
18 without computer to the same population. It means
19 that we have the same prevalence.

20 Therefore, if the prevalence is the same,
21 we can compare positive and negative predictive value
22 if we know only this fraction, like sensitivity
23 divided for one minus specificity.

24 For example, positive predictive value is
25 the same if this fraction sensitivity divided by one

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 minus specificity is the same.

2 Now I present the same information in
3 geometrical manner. Consider the plane sensitivity
4 and one minus specificity. This point presents
5 performance of reading without computer, sensitivity
6 and one minus specificity.

7 This line presents such pairs of
8 sensitivity/specificity which have the same positive
9 predictive value as positive predictive value of this
10 point.

11 This line presents such pairs of
12 sensitivity and specificity which have the same
13 negative predictive value as this point.

14 So we obtain four regions. In this
15 region, both positive and negative predictive value
16 better. In this region, both positive and negative
17 predictive worse. Therefore, if we obtain points in
18 this region, it's easy to make conclusion about this
19 point based on predictive value because in this region
20 we have both predictive value positive and in this
21 region both predictive value worse.

22 And this region unfortunately, points in
23 this region cannot -- four points in this region
24 unfortunately positive and negative predictive value
25 cannot help us because you see that the reaction of

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealgross.com

1 comparison positive and negative predictive value is
2 in opposite direction. It means that in this region
3 we still need to make some tradeoff between positive
4 and negative predictive value.

5 As you can see, that even if we have some
6 loss in specificity and some gain in sensitivity, it
7 happen that positive and negative predictive value can
8 be both better. This region, of course, very tiny,
9 but that can be that even we have loss in specificity,
10 but relatively big gain in sensitivity; then
11 predictive value can help us because they are both
12 increased.

13 Let's consider our data, comparison of
14 independent without computer and sequential with
15 computer. This point presents independent without
16 computer with the sensitivity and the specificity.
17 This point presents reading with computer, and as you
18 remember, that point estimate gives us increase in
19 sensitivity about 6.5 percent and decrease in
20 specificity about 1.7 percent.

21 You can see that this point lie almost on
22 the same line. It means that positive predictive
23 values almost the same, but this point lies above this
24 line. It means that negative predictive value is
25 better.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Therefore, we can make conclusion that
2 even the positive predictive value almost the same,
3 but negative predictive value is better for the
4 reading with computer.

5 This graph presents the changes in true
6 positive and false positive rates based on 50 percent
7 confidence rate for every one of 15 radiologists. You
8 can see that these two quadrants presents the
9 radiologists who decreased their sensitivity.

10 You can see that three -- you can see big
11 variability in the performance. Three radiologists
12 improved their performance. They increased their
13 sensitivity, both sensitivity and specificity, and one
14 radiologist have worse results because he only has
15 decrease in sensitivity without any improvement in
16 specificity.

17 This is the sensitivity and specificity
18 based on 50 percent confidence rate for secondary
19 hypothesis, small cancers from nine to 15 millimeters,
20 and you can see that point estimate for sensitivity,
21 difference point estimate, is about 10.2 percent when
22 loss in specificity 2.2 percent.

23 And if we compare with a second reading
24 with sequential without computer, then increase in
25 sensitivity is 7.4 percent when you have decrease in

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 specificity 2.4 percent. Confidence interval, wide.
2 It means that the same, the estimates, very noisy.

3 But if we apply the same argument with
4 positive and negative predictive value through this
5 situation, for example, or to this situation, then
6 it's easy to see that relatively big gain in
7 sensitivity compared to the loss in specificity gives
8 us that both positive and negative predictive value
9 are better.

10 Right now, if you remember, we are in this
11 tiny region where both predictive values are better,
12 even if we have some loss in specificity.

13 All of this previously result used only
14 information about confidence rate, not information
15 about correct location. The definition of true
16 positive based on correct location is set that cancer
17 film is considered positive with correct location if
18 the distance between the true location of cancer and
19 the radiologist mark was less than or equal to 25
20 millimeters.

21 And cancer free film is defined like false
22 positive if radiologist identified a location on this
23 film.

24 This is the result of sensitivity and
25 specificity based on correct location for primary

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 hypothesis for detection of all cancers. These three
2 columns present information about cancer films.

3 For cancer films, we can have three
4 positivities: that their mark and this mark in
5 correct location; their mark but this mark in false
6 location; and there is not any mark.

7 And for non-cancer film, we have obviously
8 two possibilities: that there are some mark, it means
9 that this is a false positive, and complementary
10 events, there is no mark.

11 You can see point estimate for the
12 difference between sensitivity -- for sensitivity
13 based on correct location, and this increase in
14 sensitivity, 2.1 percent, if we compare with first
15 reading, and loss in specificity, 2.9 percent.

16 You see that there are decrease in the
17 cancer film without marks, like 4.5 percent, but 2.4
18 percent of films has wrong location. The sum, of
19 course, the sum of all these three columns equals 100
20 percent.

21 And if we compare the reading, second
22 reading sequential without computer, then we have
23 increase in specificity like -- increase in
24 sensitivity like three percent and decrease in
25 sensitivity like 4.9 percent.

1 The confidence interval for this point
2 estimate were not provided. Therefore, this is only
3 a point estimate. It can be very noisy, but you can
4 see these results.

5 If we try to apply positive and negative
6 predictive value to this situation, then we can see
7 that this approach does not help us much because right
8 now we're in such region where, again, we need to make
9 some tradeoff between positive and negative predictive
10 value.

11 And, second, because right now we have two
12 events, one event like correct location and second
13 event like test positive or the disease is present,
14 even their definitions of positive and negative
15 predictive value can be different, and there are at
16 least three possibility variants to give the condition
17 of positive and negative predictive values.

18 The mathematical statistical area is not
19 good developed right now if we try to incorporate
20 information about location. Therefore, according to
21 the different definition of negative and positive
22 predictive value, even we cannot make that comparison
23 because if we don't know prevalence, then comparison
24 of positive and negative predictive value can be much
25 more complex.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 Therefore, in this situation you can see
2 I repeat again that positive predictive values cannot
3 help us because we see only decrease point estimate
4 like increase in sensitivity only 2.1 percent while
5 decrease in specificity, 2.9 percent.

6 This graph presents changes in true
7 positive and poor positive based on correct location
8 for every one of 15 radiologists. This green
9 quadrant, of course, we would like to see all of our
10 radiologists in this region, but reality is different.
11 You can see that some radiologists, their performance
12 even worse, and some radiologists improve their
13 performance.

14 Thank you for your attention.

15 Now Dr. Sacks will present the summary of
16 results.

17 DR. SACKS: Okay. Now, to make some sense
18 out of all of that, that's a lot of information, and
19 I'm going to try to boil it down to what we think are
20 the key points that you can sort of keep that in mind
21 and not get indigestion during lunch and be able to
22 discuss it afterward.

23 First of all, the reproducibility of the
24 device itself, as I showed, was that the mean
25 sensitivity for the three systems that they tested was

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 80 percent with a standard deviation of four and a
2 half percent, which gave a 95 percent confidence
3 interval on that sensitivity, ranging from about 71 to
4 89 percent.

5 As far as the clinical significance of the
6 clinical trial, this is rather complex and I'm going
7 to try to get it all on the screen at the same time.
8 It may help you. You've got paper copies of my
9 slides, I hope, in the mail. When we get to a pair of
10 tables, they're both on the same page, and I am not
11 going to be able to switch back and forth
12 instantaneously here. It will help you to look at
13 those. So I'm giving you a little heads up on that.

14 Now, first of all, there are three
15 possible dimensions of evaluation of the improvement
16 with the CAD. First of all, there is the
17 consideration of whether we use the location specific
18 information or the non-location specific information.

19 A second dimension is whether we use ROC
20 area or sensitivity and specificity point estimates.

21 And the third dimension is whether we use
22 the comparison of the first through the third readings
23 or the second to the third readings, and in graphical
24 form, you can see these three dimensions. There are
25 three completely different sets of conclusions.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 If I could draw a two-by-two-by-two table
2 in two dimensions, I would be glad to do it. Not
3 being able to do that, I'm going to give you the back
4 table and then the front table separately, namely, two
5 two-by-two tables.

6 So the first table is the first reading
7 compared to the third, and then I'll go on to the
8 next, which will be the second reading compared to the
9 third. So first the first compared to the third.

10 Now, we divided this, again, according to
11 location specific, which is on the left, and non-
12 location specific, which is on the right, and
13 according to whether we analyze it in terms of ROC
14 area or sensitivity of point estimates, and instead of
15 specificity or even false positive rate, which I told
16 you I preferred to specificity, what we'll look at is
17 in terms of positive predictive value.

18 Now, for the non-location specific where
19 we were able to do ROC area, because remember location
20 specific ROC analysis is currently unavailable, though
21 it may be available tomorrow or in two months or in
22 one year, but for the moment the company and we are
23 stuck not being able to use that, and the key issue
24 here is that when you do non-location specific
25 analysis, you are giving credit to a radiologist for

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

(202) 234-4433

www.nealrgross.com

1 getting it right when the radiologist thought there
2 was a cancer on the film, but thought the cancer was
3 in the left upper lobe when it was really in the right
4 lower lobe.

5 So you're giving credit for something that
6 isn't really finding the cancer.

7 Now, one can argue, yes, but you're going
8 to order a CT, and the CT will straight that out, and
9 bear that in mind. So for non-location specific ROC
10 analysis, which is the only ROC analysis we can do,
11 there was, in fact, a gain in the area under the curve
12 -- that's what Az means -- for all the cancers, as
13 well as for the small cancers, but there was not, at
14 least using the first to the third, for the priors,
15 that is, not a statistically significant gain.

16 If we come down to the estimates, the
17 point estimates, of sensitivity and positive
18 predictive value, the gain in sensitivity for all
19 cancers, and we'll look at the small cancers as well,
20 was from 71 to 78 percent. This was not statistically
21 significant. Although it looks large, it did not have
22 the statistical significance for the first to third
23 readings. It will when we see the next slide.

24 On the small cancers, however, the
25 increase in sensitivity -- again, this was used at the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 50 percent point on the ROC curve -- went from 64
2 percent on average for the radiologist up to 74
3 percent, and that is statistically significant, though
4 we don't have the error bias here. I'm just
5 summarizing what you've already seen.

6 The net result was that there was a rise
7 in positive predictive value, and the importance of
8 that is -- I'm going to skip ahead two slides here for
9 a second, and while this looks a little busy, I think
10 it's going to help. There's a statement of faith.

11 (Laughter.)

12 DR. SACKS: If we suppose that this is our
13 starting operating point and here is the ROC curve
14 without the CAD and the upper one is the ROC curve
15 with the CAD; if we suppose that this is our starting
16 50 percent operating point without CAD, there are any
17 number of different possibilities that we could have
18 seen with the data in terms of where does it move with
19 the CAD.

20 It could have moved up and to the left.
21 It could have moved along this line of constant
22 positive predictive value. It could have moved along
23 the same ROC curve. It could have moved along a line
24 of what Dr. Kondratovich has shown you is a line of
25 constant negative predictive value, but just as with

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701