

UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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RADIOLOGICAL DEVICES PANEL

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MEETING

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TUESDAY, DECEMBER 10, 2001

The Panel met at 8:30 a.m. in the Walker/Whetstone Rooms of the Gaithersburg Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, Maryland, Dr. Minesh P. Mehta, Chairman, presiding.

PRESENT:

MINESH P. MEHTA, M.D.	Chairman
HARRY K. GENANT, M.D.	Member
GEOFFREY S. IBBOTT, Ph.D.	Member
ALICIA Y. TOLEDANO, Sc.D.	Member
PRABHAKAR TRIPURANENI, M.D.	Member
EMILY F. CONANT, M.D.	Temporary Voting Member
REGINA J. HOOLEY, M.D.	Temporary Voting Member
MARILYN R. PETERS, M.N., M.P.H.	Non-Voting Consumer Representative
ERNEST L. STERN	Non-Voting Industry Representative
ROBERT J. DOYLE	Executive Secretary

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

8:33 a.m.

1
2
3 CHAIRMAN MEHTA: I think if everybody will
4 take a seat, we would like to go ahead and get started
5 on time. Several people have come from long
6 distances, and we would like to stay on time today, if
7 possible.

8 So I would like to call this meeting of
9 the Radiological Devices Panel to order. I also want
10 to request everyone in attendance at the meeting to
11 sign in on the attendance sheet that's available at
12 the door.

13 For the record, I note that the voting
14 members present constitute a quorum, as required by 21
15 CFR Part 14, and at this time I would like to have
16 each of the Panel members at the table to introduce
17 themselves, state their specialty, position title,
18 institution, and status on the Panel.

19 I'll begin with myself. My name is Minesh
20 Mehta. I'm a radiation oncologist at the University
21 of Wisconsin, and I'm currently the Chair of the
22 Radiological Devices Panel.

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1 We'll move to the right and we'll have
2 individuals introduce themselves, and we'll go around
3 the table and come back, so that the introductions are
4 complete.

5 DR. CONANT: Good morning. I'm Emily
6 Conant, and I'm Chief of Breast Imaging at the
7 University of Pennsylvania, Associate Professor, and
8 I'm here as, I think, a clinical breast imager.

9 DR. HOOLEY: Hello. My name is Regina
10 Hooley. I'm an Assistant Professor of Diagnostic
11 Radiology at Yale University with a specialty in
12 mammography. I'm here as a consultant as a breast
13 imager.

14 DR. IBBOTT: I'm Geoff Ibbott. I'm a
15 medical physicist, and I'm an Associate Professor at
16 MD Anderson Cancer Center in the Department of
17 Radiation Physics there. I'm also Director of the
18 Radiological Physics Center at MD Anderson, and I'm a
19 member of the Panel.

20 MR. STERN: My name is Ernie Stern. I'm
21 the industry representative. I'm the Chairman of
22 Thales Components Corporation, the U.S. subsidiary of

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1 Thales in France. We manufacture defense electronics
2 and medical electronics products.

3 DR. TRIPURANENI: I'm Prabhakar
4 Tripuraneni, radiation oncologist by training and
5 trade. I'm the head of the Radiation Oncology at
6 Scripps Clinic in La Jolla, California, and I'm a
7 Panel member.

8 MS. BROGDON: Good morning. I'm not a
9 member of the Panel. I'm Nancy Brogdon. I'm the
10 Director of FDA's Division of Reproductive, Abdominal,
11 and Radiological Devices.

12 MS. PETERS: I'm Marilyn Peters. I'm a
13 consumer representative, and I'm a health education
14 consultant in Los Angeles.

15 DR. GENANT: Good morning. I'm Harry
16 Genant. I'm a radiologist. I'm Professor of
17 Radiology Medicine and Orthopedic Surgery at the
18 University of California, San Francisco, and the
19 Executive Director of the Osteoporosis and Arthritis
20 Research Group at UCSF. I'm a Panel member.

21 DR. TOLEDANO: Good morning. My name is
22 Alicia Toledano. I'm Assistant Professor at the

1 Center for Statistical Sciences at Brown University.
2 My specialty is with diagnostics, diagnostic
3 radiology, and I am a Panel member.

4 MR. DOYLE: And my name is Bob Doyle. I'm
5 the Executive Secretary of this Panel.

6 CHAIRMAN MEHTA: Thank you, everybody.

7 At this time Dr. Robert Phillips, the
8 Chief of the Radiology Branch of the Office of Device
9 Evaluation, would like to give us a brief update on
10 the FDA radiological activities over the past several
11 months.

12 Dr. Phillips?

13 DR. PHILLIPS: Good morning. It's a
14 little chilly out, I think, isn't it?

15 (Laughter.)

16 I want to give you an update of what has
17 happened as far as our major approvals since the last
18 time we met. If you recall, the last meeting of the
19 Panel was in March 2001.

20 Since then, we have approved for marketing
21 the following devices:

22 Sirtex, which was Sirspheres, which is a

1 brachytherapy product for treatment of liver cancers.
2 This is an injectable, and I believe this was brought
3 to the Panel some time ago.

4 Deus Technologies, which makes a rapid-
5 screen CAD which is used for detecting solitary
6 nodules in the lung from a flat-film lung x-ray.

7 Diagnostic Medical Systems, the UBIS Bone
8 Sonometer. This is another bone sonometer. You know,
9 we have seen several of these, and the Panel looked at
10 one of these quite some time ago.

11 We've approved the Fisher Imaging
12 Corporation's SenoScan, which is a full-field digital
13 mammography system.

14 We've also approved the Lorad Digital
15 Breast Imager, which is also a full-field digital
16 mammography system.

17 And then the CADx Medical Systems, which
18 is a second look. It's used as a second look for
19 breast mammography.

20 And the same thing for Intelligent Systems
21 Software, which is a MammoReader CAD. Again, it is a
22 second look or back-up CAD system for digital

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1 mammography.

2 Along with that, we have approved
3 supplements for Soft Copy Imaging for the Digital
4 Mammography Systems.

5 All of the PMAs that we have have
6 summaries of safety and effectiveness. If anybody on
7 the Panel is interested in any of these, if you would
8 just drop me a line or leave me a note, I will be glad
9 to send them to you, so you can see what our basis for
10 approval was.

11 Thank you. Any questions?

12 CHAIRMAN MEHTA: Any questions for Dr.
13 Phillips?

14 (No response.)

15 No? Thank you, Dr. Phillips.

16 At this time Mr. Doyle would like to make
17 some introductory remarks.

18 MR. DOYLE: Thank you, Dr. Mehta.

19 Pursuant to the authority granted under
20 the Medical Devices Advisory Committee charter, dated
21 October 27th, 1990, and as amended August 18th, 1999,
22 I appoint the following individuals as voting members

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1 of the Radiological Devices Panel for the meeting of
2 December 10th, 2002. These individuals are Emily F.
3 Conant, M.D., and Regina J. Hooley, M.D.

4 For the record, these individuals are
5 special government employees and consultants to this
6 Panel under the Medical Devices Advisory Committee.
7 They have undergone the customary conflict-of-interest
8 review and have reviewed the material to be considered
9 at this meeting. This authorization is signed by
10 David W. Feigal, Jr., Director, Center of Devices and
11 Radiological Health.

12 Now for the conflict-of-interest, the
13 following announcement addresses conflict-of-interest
14 issues associated with the meeting and is made part of
15 the record to preclude even the appearance of an
16 impropriety.

17 To determine if any conflict existed, the
18 agency reviewed the submitted agenda and all financial
19 interests reported by the Committee participants. The
20 conflict-of-interest statute prohibits special
21 government employees from participating in matters
22 that could affect their employer's financial

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1 interests. However, the agency has determined that
2 participation of certain members and consultants, the
3 need for whose services outweighs the potential
4 conflict-of-interest involved, is in the best interest
5 of the government.

6 Therefore, waivers have been granted to
7 Drs. Regina Hooley, Geoffrey Ibbott, and Prabhakar
8 Tripuraneni for their interest in firms that could
9 potentially be affected by the Panel's
10 recommendations. The waivers allow them to
11 participate fully in today's deliberations.

12 Dr. Hooley's waiver involves stockholdings
13 valued between \$25,001 to \$50,000 in the parent of a
14 competing technology manufacturer.

15 Dr. Ibbott's waiver involves a consulting
16 arrangement with a competing technology firm. For
17 this unrelated consulting services, he receives less
18 than \$10,000 a year.

19 Dr. Tripuraneni's waiver involves an
20 unrelated consulting agreement with a firm that has a
21 financial interest in a competing technology
22 manufacturer. He receives less than \$10,000 a year

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1 for this service.

2 Copies of these waivers may be obtained
3 from the agency's Freedom of Information Office, Room
4 12A-15 of the Parklawn Building.

5 We would like to note for the record that
6 the agency took into consideration other matters
7 regarding Drs. Ibbott, Mehta, and Tripuraneni. They
8 reported interest in firms at issue, but in matters
9 not related to today's agenda. The agency has
10 determined, therefore, that they may participate fully
11 in all discussions.

12 In the event that the discussion involves
13 any other products or firms not already on the agenda
14 for which an FDA participant has a financial interest,
15 the participant should excuse him or herself from such
16 involvement, and the exclusion will be noted for the
17 record.

18 With respect to all other participants, we
19 ask, in the interest of fairness, that all persons
20 making statements or presentations disclose any
21 current or previous financial involvement with any
22 firm whose products they wish to comment upon.

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1 If anyone has anything to discuss
2 concerning these matters, please advise me now, and we
3 will leave the room to discuss them.

4 (No response.)

5 Seeing none, I will proceed.

6 The FDA seeks communication with industry
7 and the clinical community in a number of different
8 ways. First, FDA welcomes and encourages pre-meetings
9 with sponsors prior to all IDE and PMA submissions.
10 This affords the sponsor an opportunity to discuss
11 issues that could impact the review process.

12 Second, the FDA communicates through the
13 use of guidance documents. Towards this end, FDA
14 develops two kinds of guidance documents for
15 manufacturers to follow when submitting a pre-market
16 application.

17 One type is simply a summary of
18 information that has historically been requested on
19 all devices that are well-understood in order to
20 determine substantial equivalence.

21 The second type of guidance document is
22 one that develops as we learn about new technology.

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1 The FDA welcomes and encourages the Panel and industry
2 to provide comments concerning our guidance documents.

3 I would also like to remind you that the
4 next two meetings of the Radiological Devices Panel
5 are tentatively scheduled for February 4th and March
6 20th next year. You may wish to pencil these dates on
7 your calendar, but please recognize that these dates
8 are tentative at this time.

9 Thank you.

10 MS. BROGDON: Excuse me, Mr. Doyle. You
11 said March 20th for the next meeting?

12 MR. DOYLE: May. Did I say March? Oh,
13 excuse me. Thank you. May 20th.

14 CHAIRMAN MEHTA: Thank you for the
15 correction, Nancy.

16 Thank you, Mr. Doyle.

17 The first item on our agenda today is a
18 presentation by Dr. Stanley Stern from the Office of
19 Surveillance and Biometrics. Dr. Stern will discuss
20 the development of amendments to the U.S. Radiation
21 Safety Standards for diagnostic x-ray computed
22 tomography.

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1 DR. STERN: Thank you very much. Just a
2 minor correction: I'm from the Office of Health and
3 Industry Programs, and the Office of Surveillance and
4 Biometrics is kindly sponsoring this presentation.

5 The presentation is provided solely for
6 your information. It grows out of the collaborative
7 efforts of an FDA group of science, regulation, and
8 economics staff. We're working to facilitate
9 radiation dose reduction through consideration of
10 amendments to the existing CT Equipment Radiation
11 Safety Performance Standard.

12 I just might mention, by the way, today
13 was published in The Federal Register proposed
14 amendments to the X-Ray Performance Standard.

15 The Work Group's current thinking and my
16 own personal views and analysis here, presented here,
17 don't necessarily reflect any official position of the
18 FDA or any of its components. Many items in the
19 slides are annotated with superscripted numbers that
20 refer to citations and notes listed at the end of the
21 presentation. Reference to any products,
22 manufacturers, models of CT systems, or external

1 websites does not imply FDA endorsement.

2 Computer tomography is a vitally-
3 important, beneficial modality whose radiation doses
4 are relatively higher than those of other x-ray exams.
5 The scope of CT applications is broad, and CT is used
6 in many different ways, from diagnosis to staging, to
7 treatment planning, and, more recently, for real-time
8 visualization during interventional operations.

9 Our motivation is the proposition that the
10 current federal regulations covering CT, in place
11 since the mid-1980s, have not kept pace with
12 technological developments and with the need to assure
13 the lowest dose for the best image quality practically
14 achievable.

15 What is prompting us to consider updated
16 standards? The items on the lefthand of this slide
17 underscore some post-market public health concerns
18 ensuing from the growth and use of CT. The righthand
19 side lists the preliminary responses of CDRH in
20 addressing these concerns.

21 First, we are faced with the problem of
22 determining the scope of radiological exposure from

1 CT. How many CT examinations are going on annually?
2 And just how large are the doses from what particular
3 exams?

4 CDRH provided the principal technical
5 direction for a survey conducted through the
6 nationwide evaluation of X-Ray Trends Program,
7 administered by the Conference of Radiation Control
8 Program Directors.

9 Between April 2000 and July 2001, state
10 inspectors surveyed examination doses and workloads in
11 263 CT facilities randomly selected in 39 states to
12 provide the first national understanding of the
13 magnitude of collective dose from CT since the first
14 CT survey in 1990.

15 A related project is the ongoing
16 development of a handbook of patient doses associated
17 with approximately 50 of the most common CT
18 examinations. Such a handbook would force the risk
19 communication between medical staff and patients, and
20 it would enable medical physicists and radiologists to
21 evaluate patient tissue doses and effective dose for
22 their facility's CT systems and adjust their protocols

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1 that CT techs follow in order to reduce doses.

2 In February 2001, The American Journal of
3 Roentgenology published a series of papers describing
4 the potential risk associated with inappropriate
5 equipment settings and scanning techniques in CT
6 examinations of children. A great deal of publicity
7 resulted from these studies and our concerns were
8 voiced at the 2001 meeting of the Technical Electronic
9 Product Radiation Safety Standards Committee. That's
10 the advisory committee to the FDA.

11 Following that Committee's recommendation,
12 in November 2001, CDRH issued a public health
13 notification to radiologists, radiation health
14 professionals, risk managers, and hospital
15 administrators alerting facilities to the problem and
16 providing practical advice on how to reduce risks
17 associated with CT dose in pediatric and small adult
18 patients.

19 Following up, FDA was active in planning
20 and participating in an NCI-sponsored Symposium on
21 Patient Dose held just five weeks ago by the National
22 Council on Radiation Protection and Measurements.

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1 There's been burgeoning popularization of
2 a group of applications commonly referred to as CT
3 screening of self-referred individuals who are
4 asymptomatic of any particular disease. Among these
5 applications include whole body examinations,
6 examinations of the lungs for cancer, and calcium
7 scoring of the heart as a purported indicator of
8 potential heart disease.

9 Right now CT screening makes up only a
10 tiny fraction of the number of CT procedures performed
11 annually in the U.S. Our main concerns are the risks
12 associated with false positive results and with
13 radiation dose.

14 False positive results could needlessly
15 lead to follow-up tests or procedures that might be
16 invasive associated with surgical risks of anesthesia,
17 bleeding, infection, scarring, or entail additional
18 radiological exams.

19 Radiation doses and diagnostics CT are
20 among the highest of those of all x-ray modalities,
21 and screening CT doses are significantly large, even
22 when low-dose protocols might be applied.

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1 There are no scientific studies
2 demonstrating that whole body CT screening of
3 asymptomatic people is efficacious. Were it a useful
4 screening test, it would be able to detect particular
5 diseases early enough to be managed, treated, or cured
6 and advantageously spare a person at least some of the
7 detriments associated with serious illness or
8 premature death.

9 At this time any such presumed benefit of
10 whole body CT screening is, in fact, uncertain, and
11 the benefit may not be great enough to offset the
12 potential harm such screening could cause.

13 Last April FDA posted a web page about CT
14 screening. The page provides information about our
15 concerns. It contains brief explanations of computer
16 tomography, radiation risks, radiation quantities and
17 units, the regulatory status of CT, and includes links
18 to related resources.

19 It's hoped that an objective presentation
20 from a government institution whose fundamental
21 mission is to protect public health will clarify the
22 natures of the risks and presumed benefits in a way

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1 that persuades people to carefully consider these
2 aspects of CT screening before deciding whether or not
3 to have such exams.

4 Finally, we are aware of the small, but
5 growing, use of what's called CT fluoroscopy or
6 dynamic CT to visually guide interventional procedures
7 and those involving biopsy, drainage, device
8 placement. CT fluoroscopy refers to the capability of
9 a CT system to update images in nearly real time, as
10 the x-ray field and detectors rotate multiple times
11 around the patient at a fixed z-position; that is,
12 without table movement.

13 In general, interventional fluoroscopic
14 procedures are a concern with respect to large
15 radiation dose, all the more so, as often as not, they
16 may be performed by physicians in a broad range of
17 specialties outside of radiology, physicians who may
18 not have had particular training in radiation safety.
19 Hence, equipment features that tend to reduce dose
20 systematically automatically, irrespective of
21 professional background, might be desirable.

22 Recent reports cite mean values of

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1 entrance skin dose of approximately 100 to 400
2 milliGray, below the threshold for skin injury.
3 Several years ago a small CDRH group did guidance for
4 reviewers and manufacturers of CT systems capable of
5 CT fluoroscopy, but to move to formal adoption, a
6 final guidance has been on hold in view of the
7 relatively small probability for skin injury in the
8 most common procedures, and also since preliminary
9 findings of the 2000 CT survey indicated that only 5
10 percent of the most frequently-used CT units and
11 facilities have the capability of doing CT fluoroscopy
12 in the first place.

13 The baseline of radiation with respect to
14 CT equipment is prescribed by the federal government
15 through performance standards established under the
16 Radiation Control for Health and Safety Act. The
17 regulations in place now date back approximately 20
18 years. These rules apply to manufacturers of CT
19 equipment, not to the facilities that use the
20 equipment.

21 The basic mandate is documentary.
22 Manufacturers must provide users with specified

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1 documentation of dose values for CT systems under
2 typical operating conditions. Because this mandate
3 predates special or new modalities, such as electron
4 beam, multi-slice, spiral, fluoroscopic, or cone beam
5 CT, the doses manufacturers report don't necessarily
6 pertain to those modes of operation. There is no
7 regulatory ceiling on patient dose, and there are few
8 major equipment requirements particular to CT per se.

9 Possible amendments to the current
10 Radiation Safety Performance Standard would require
11 particular technical features for CT equipment. The
12 initial focus of the Work Group effort is on three
13 possible features:

14 One, display and recording of standardized
15 dose indices. Two, automatic control of x-ray
16 exposure according to individual patient thickness,
17 and, three, x-ray field-size limitation for multi-
18 slice systems.

19 This amendment would require each new CT
20 system to provide users with options to display and
21 record one or more dose indices for every patient's
22 examination. The dose indices and related terminology

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1 would be standardized through formal definition and
2 regulations.

3 An example is the volume Computed
4 Tomography Dose Index, which is the CTDI, corrected
5 for scanning with gaps between slices or scanning with
6 overlapping slices. Another example is the dose-
7 length product which is proportional to the length of
8 the patient volume scanned in an exam.

9 Such an amendment would enable an aspect
10 of facility quality assurance that today is feasible
11 only with extra effort or through features available
12 on just some newer scanner models. The basis of this
13 quality assurance is the use of what are called
14 reference dose values as norms to which individual
15 examination doses could be compared.

16 If reference values are exceeded,
17 facilities could follow up anomalies by looking at
18 possible problems to see if exposures could be reduced
19 without compromising image quality. A reference dose
20 value corresponds to the 75th percentile of the
21 distribution of measured dose values for particular
22 radiological procedures. Reference values may be

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1 generated based on a facility's own records of dose
2 distributions for various CT exams or based on
3 regional or national dose distributions.

4 Recent experience in the United Kingdom
5 leads us to assume that the systematic use of dose
6 index display or recording in a facility audit program
7 could reduce patient CT dose on average on the order
8 of 15 percent.

9 Of the three technical areas that we are
10 considering, probably the largest dose reduction, at
11 least for thinner patients, would be brought about by
12 requiring every newly-manufactured CT system to
13 provide the capability of automatically adjusting the
14 amounts of x-ray emissions into those needed to image
15 particular patient anatomy.

16 In other words, as the x-ray beam probes
17 a thinner portion of the anatomy, which would not
18 require as much radiation as a thicker portion would
19 in order to reach the detectors, the CT system would
20 automatically reduce the average tube current or
21 voltage or some combination of radiological variables
22 to spare that thinner part unnecessary dose.

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1 Conversely, when the beam encounters thicker anatomy,
2 the CT system would automatically increase the tube
3 output to levels needed for adequate visualization.

4 An automatic exposure control system
5 offers a technical answer to facilities where, for
6 practical or clinical reasons, it is not the practice
7 to change manual techniques on a patient-by-patient
8 basis, let alone readjust techniques within a single
9 patient exam.

10 With an AEC system in place, the
11 presumption is that pediatric and thinner adult
12 patients would receive lower doses than thicker
13 patients. Calculations and measurements suggest that
14 use of a sophisticated automatic exposure control
15 system could reduce patient dose by approximately 30
16 when compared to systems where the techniques are set
17 manually.

18 We are concerned that a number of
19 different multi-slice CT models produce images with a
20 technologically-inefficient application of radiation.
21 This inefficient technology has been dubbed
22 "overbeaming."

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1 The two figures represent a comparison of
2 the spatial distributions of radiation incident on a
3 patient. The figure on the left depicts the
4 distribution for a single-slice CT scanner, whereas
5 the one on the right corresponds to that of a multi-
6 slice scanner.

7 Here's the important point in this
8 comparison: Although the amount of radiation applied
9 to construct one image with the single-slice scanner
10 or to construct a set of images with the multi-slice
11 system is the same for each configuration, for the
12 multi-slice CT system the radiation distribution is
13 much wider than that of the single-slide system.

14 Why? Multi-slice CT imaging requires that
15 radiation incident on the patient be consistently
16 distributed across each of the separate areas
17 subtended by the detectors. Such consistency can be
18 achieved by opening up the z-collimation of the source
19 radiation so that only the most spatially-uniform
20 region of the x-ray field, the umbra, is subtended by
21 the detectors.

22 Furthermore, since the x-ray focal spot

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1 tends to wander around spatially, multi-slice models
2 broaden the umbra by opening the collimation even more
3 to compensate for x-ray source excursions. All of the
4 radiation that falls beyond the spatial extent of the
5 detectors is not used by the detectors for image
6 construction, but it is, nevertheless, incident on the
7 patient and contributes to the dose.

8 To mitigate the inefficient use of
9 radiation in multi-slice computed tomography, we
10 suggest consideration of an x-ray field-size
11 limitation. Such an amendment would require that all
12 new CT systems be capable of automatically limiting
13 field sizes to those no larger than needed to
14 construct multi-slice images. Several technical
15 approaches to enable such limitation have been
16 patented, and one, in fact, has been implemented.

17 The approach implemented uses some of the
18 x-ray detectors lying behind those capturing the
19 clinically-useful signal to track the wandering of the
20 penumbral regions of the x-ray field and feed back
21 instructions to motor-driven collimator cams to
22 readjust their positions. The result is that the

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1 umbra remains subtended by the clinical signal
2 detectors.

3 The chart on the right depicts two multi-
4 slice dose profiles measured in a head phantom on the
5 same CT system. For the same 5-millimeter-wide
6 imaging sensitivity profile, the dose profile in black
7 is obtained when there is no tracking and collimation
8 update system, whereas the dose profile in fuchsia is
9 obtained when the tracking update system is activated.

10 It is evident that the non-tracking dose
11 profile is approximately 50 percent wider than the
12 tracking profile. All of the radiation represented by
13 the difference between the two profiles would
14 correspond to radiation which is absorbed by a
15 patient, but not used to construct images. Data
16 suggests that the kind of x-ray field-size limitation
17 enabled by tracking collimation adjustment could
18 reduce dose in multi-slice CT systems on the order of
19 30 percent.

20 If all CT equipment were to include the
21 technical features just proposed for consideration as
22 mandatory standards, then, based on the relative dose

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1 reductions and the collective dose attributable to CT,
2 one can estimate an annual collective dose savings of
3 193,000 person-Sieverts per year. For an annual
4 collective dose savings of 193,000 person-Sieverts, on
5 the order of 870,000 radiation-induced cancer
6 mortalities are projected to be avoided per year,
7 beginning 20 years after each annual collective
8 exposure.

9 The yellow shading is intended to
10 highlight the uncertainty in this projection, which is
11 based on an extrapolation to the CT dose region of a
12 mortality risk estimate derived from larger-dose
13 epidemiological data. Other methods of extrapolation
14 could yield higher or lower estimates of the number of
15 radiation-induced cancer deaths, and it is conceivable
16 that the estimated dose savings would not result in
17 any significant avoidance of cancer death at all.

18 In the United States in the year 2000 the
19 annual number of deaths linked to cancer from all
20 causes not specifically associated with radiation is
21 approximately 550,000. There would also be a
22 significant benefit and pecuniary savings associated

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1 with society's willingness to pay to avoid mortality
2 risk, and economists have estimated that society pays
3 on the order of \$5 million per premature mortality
4 that it perceives might be avoided.

5 We have come up with a framework for
6 analysis that will lead to what is called the Concept
7 Paper for possible development of amendments. That is
8 an internal document which will be the basis for CDRH
9 decisions on how to proceed.

10 In the block on the right, the green
11 shading indicates the technical areas summarized in
12 this presentation, and the red shading contains areas
13 where we have an interest that is deferred for the
14 time being. The yellow-shaded block on the left lists
15 some general categories of issues: technical
16 feasibility, impact on clinical aspects such as
17 efficacy, frequency of utilization, harmonization with
18 international consensus standards, CDRH resources
19 required to develop test methods and to incorporate
20 the administration of new rules in a compliance
21 program. The arrows indicate that in principle each
22 of these issues can be applied as a basis of

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1 assessment to each technical area under consideration.

2 Although the equipment features that I
3 have discussed today may all be technically-feasible,
4 there remain a number of particular problems
5 outstanding. Here are a few examples:

6 First, for the purpose of display or
7 recording in a quality assurance program, not only
8 would we have to select a representative index of
9 patient dose, we would need to specify whether the
10 dose index could be based on average values,
11 determined by manufacturers for all models of
12 scanners, or whether it must be specific to the
13 particular unit actually being used in a facility.

14 Perhaps the dose index displayed or
15 recorded could be based on real-time measurements made
16 during actual patients' examinations. It is not clear
17 how the index would represent values in an automatic
18 exposure control mode. Parameters based on CTDI may
19 not be good candidates to represent skin dose,
20 particularly for CT fluoroscopy. A good skin dose
21 index may need to be developed. A recording
22 capability for a dose index may affect practice and

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1 use, and we ought to consider such impact.

2 Second, with respect to automatic exposure
3 control, in addition to specifying what kind of
4 technological approach is best, perhaps the key issue
5 is how to define the optimal amounts of radiation
6 needed by the detectors for particular imaging tasks.
7 These amounts would effectively set the points of
8 detection equilibrium, driving the modulation of
9 emissions from the x-ray source according to patient
10 anatomy thickness.

11 Perhaps we need to set standards to
12 optimize detection. It's not clear who --
13 manufacturers, radiologists, FDA -- should set the
14 equilibrium points and how that would be done.

15 In a related issue, Philip Judy, a
16 prominent medical physicist, cautioned that while
17 automatic exposure control may reduce dose to thinner
18 patients, it also might on average increase dose to
19 thicker patients.

20 Third, a primary challenge in developing
21 an amendment for x-ray field-size limitation or for
22 automatic exposure control, and most likely other

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1 areas as well, would be how to prescribe performance
2 standards, not design standards, forward-looking
3 enough to transcend limitations that might be present
4 in current technological approaches.

5 In conclusion, an FDA Work Group has
6 identified several areas of possible development of
7 mandatory CT equipment radiation safety performance
8 standards. The initial focus is on technically-
9 feasible features that would reduce patient dose; dose
10 index standardization; display and recording;
11 automatic exposure control, and x-ray field-size
12 limitation.

13 Were these features implemented on all CT
14 systems, the projected collective dose savings in the
15 United States would be approximately 193,000 person-
16 Sieverts yearly. The Work Group has established a
17 framework of issues for analysis that would be
18 detailed in a regulatory concept paper for internal
19 decisions on how to proceed. We expect industry,
20 professional groups, and states to contribute to our
21 development process.

22 Our timeline for the initial stage of this

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1 process is to begin a Concept Paper by the end of this
2 year, and next year brief the FDA Advisory Committee,
3 the Technical Electronic Product Radiation Safety
4 Standards Committee, from whom we would seek further
5 recommendations.

6 I thank you for your attention.

7 CHAIRMAN MEHTA: Thank you, Dr. Stern.

8 Any questions for Dr. Stern?

9 (No response.)

10 Thank you.

11 I think we are about five to ten minutes
12 early, but we will get started early. That will give
13 us an opportunity to devote enough time to the primary
14 agenda of today's meeting, which I did not state at
15 the beginning. So I'll restate that for the record.

16 So the purpose of the meeting is to
17 discuss, make recommendations, and vote on a pre-
18 market approval application, PMA P010035, for a device
19 that produces a computerized thermal image of the
20 breast of women recommended for biopsy.

21 We'll begin the public hearing session of
22 the meeting. This will be the first of two half-hour

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1 open public hearing sessions for this meeting. The
2 second half of our open public hearing session will
3 follow the Panel discussion later this afternoon. At
4 these times, public attendees are given an opportunity
5 to address the Panel to present data or views relevant
6 to the Panel's activities.

7 It is my understanding that no individual
8 has given advance notice of wishing to address the
9 Panel. If there is anyone now wishing to address the
10 Panel, please identify yourself at this time.

11 (No response.)

12 Seeing none, I would like to remind the
13 public observers at this meeting that, while this
14 portion of the meeting is open to public observation,
15 public attendees may not participate except at the
16 specific request of the Chair.

17 I would like at this time that persons
18 addressing the Panel now or later to come forward to
19 the microphone and speak clearly, as the
20 transcriptionist is dependent on this for providing an
21 accurate transcription of the proceedings of the
22 meetings.

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1 If you have a hard copy of your talk
2 available, please provide it to the Executive
3 Secretary, so that they can use this and the
4 transcriptionist can help provide an accurate record
5 of the proceedings.

6 We are also requesting that all persons
7 making statements either during the open public
8 hearings or the open Committee discussion portions of
9 the meeting to disclose if they have financial
10 interests in any medical device company. Before
11 making your presentation to the Panel, in addition to
12 stating your name and affiliation, please state the
13 nature of your financial interest and the organization
14 you represent. Of course, no statement is necessary
15 from employees of the sponsoring organization.

16 Definition of financial interests in the
17 sponsor company may include compensation for time and
18 services of clinical investigators, their assistants
19 and staff, in conducting the study and in appearing at
20 the Panel meeting on behalf of the applicant; a direct
21 stake in the product under review -- for example,
22 inventor of the product, patentholder, owner of shares

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1 of stocks, et cetera, or owner or part-owner of a
2 company.

3 We can now begin the first open public
4 portion of this meeting. We will begin with
5 presentations on P010035 by the sponsor.

6 So this will conclude the open public
7 portion of the meeting. We will now begin the open
8 Committee discussion. Again, this is for PMA 0100035,
9 for a device that produces a computerized thermal
10 image of the breast of women recommended for biopsy.

11 The sponsor, Computerized Thermal Imaging,
12 Inc., CTI, will state its case for the PMA and be
13 followed by the FDA presentations.

14 The first speaker will be John Brenna, the
15 President and CEO of CTI.

16 MR. BRENNNA: Good morning. My name is
17 John Brenna. I would like to thank the members of the
18 Panel Review Board, the Food and Drug Administration,
19 ladies and gentlemen from the press, and the general
20 public for the opportunity today to introduce CTI's
21 breast imaging system known as the BCS 2100.

22 This is a non-invasive, adjunctive device

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1 that's designed to work with mammography to obviate
2 biopsy of benign masses. It's a system that provides
3 physiological information based on infrared technology
4 that supplements the anatomical information provided
5 by mammographic x-ray.

6 Before I introduce the other members of
7 the team, I would like to take a few moments to
8 highlight some of the key points about this device
9 that you will be hearing about in more detail in the
10 following presentations.

11 This is a diagnostic breast imaging system
12 that provides a painless, non-invasive patient
13 procedure, a procedure that takes less than ten
14 minutes to complete, that captures over 100 dynamic
15 images and collects over 8.3 million temperature
16 values per imaged breast. It is adjunctive to
17 mammography x-ray and it provides physiological
18 information.

19 A clinical manuscript describing the
20 clinical trials of the BCS 2100 has been reviewed and
21 accepted for peer review and will be published by The
22 American Journal of Roentgenology, which is scheduled

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1 later this month.

2 Our product focus is to market the BCS
3 2100 exclusively to MQSA-certified facilities and
4 under control of Board-certified radiologists.

5 Now I would like to take the time to
6 introduce the members of the CTI presentation team,
7 and from the CTI organization I would like to
8 introduce Lynn Satterthwaite, our Vice President of
9 Engineering. Lynn, would you stand up?

10 Dr. Karleen Callahan, the Director of
11 Clinical Research.

12 I also would like to introduce our
13 principal investigators, Dr. Yuri Parisky, Associate
14 Professor of Radiology from the University of Southern
15 California School of Medicine, also a Director of
16 Breast Imaging Services at USC/Norris Comprehensive
17 Cancer Center in Los Angeles, and was a principal
18 investigator during the clinical trials. Dr. Parisky.

19 I also would like to introduce Kevin
20 Hughes, Assistant Professor of Surgery, the Harvard
21 Medical School; Surgical Director of Breast Screening
22 at the Massachusetts General Hospital, and also a

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1 principal investigator at the Lahey Clinic. Dr.
2 Hughes.

3 Advisors to the CT organization include
4 Dr. Kathy Plesser, former Chief of Breast Imaging at
5 St. Vincent's Comprehensive Cancer Center in New York.
6 Not joining us today, but an advisor to the
7 organization is Dr. Pat Romilly, Assistant Professor
8 of Radiology at H. Lee Moffitt Cancer Center.

9 Other advisors: Dr. Steven Rust, Senior
10 Research Leader from the Battelle Institute. Steve.
11 Dr. Loraine Sinnot, Research Scientist at the Battelle
12 Institute, and Elizabeth Nelson, a Senior Regulatory
13 Consultant from the Catalyst Group.

14 Our agenda today will cover the following
15 topics: Dr. Parisky will lead off with a presentation
16 regarding the clinical environment, followed by a
17 presentation by Dr. Hughes on patient management and
18 case presentations, a device description and an
19 operation -- and you may note off to your right we do
20 have a system with us to demonstrate during the break
21 periods -- followed by a clinical trial process and
22 statistical procedures presentation by Dr. Callahan,

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1 and a wrapup on the efficacy of results and
2 indications for use by Dr. Parisky.

3 Thank you.

4 DR. PARISKY: Thank you very much, John.
5 Thank you. It's good to meet distinguished members of
6 the Panel as well as members of the audience.

7 I'll give you a brief perspective on
8 mammography and diagnostic breast imaging; I'm sure
9 most of you are familiar with it. Mammography made
10 its introduction in the sixties with subsequent
11 development of film screen mammography for the purpose
12 of detecting occult or clinically-occult breast
13 cancer. The majority of abnormalities at that time
14 went to biopsy, most likely surgical biopsy.

15 The introduction and proliferation of
16 diagnostic mammography with specialized views,
17 unfortunately, did not add significant sensitivity or
18 specificity and did not detract significantly from the
19 biopsy rates.

20 The introduction of ultrasound within the
21 past decade introduced an early drop in the number of
22 breast biopsies performed because of the recognition

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1 of cysts, but now the proliferation of ultrasound-
2 guided biopsies have led to an increase in biopsies of
3 abnormalities detected.

4 Other modalities have been introduced and
5 are discussed in literature and at scientific
6 conferences, notably Sestamibi, PET scan, MRI. All of
7 these modalities advocate or publish sensitivities in
8 the high eighties to low nineties with specificities
9 ranging anywhere from the twenties to the eighties.

10 The ethical imperative I have as a full-
11 time clinical diagnostic radiologist who practices in
12 breast imaging is to do no harm to the patient. My
13 job is to detect breast cancer with at the same time
14 the imperative to do no harm by unnecessarily
15 biopsying the patient.

16 Every year at least 1.3 million to maybe
17 upwards of 1.5 million women undergo breast biopsies
18 to determine if they have cancer of the breast. At
19 least 80 percent of these biopsies are benign. That
20 means over a million women undergo a procedure for
21 benign process.

22 There are a number of inconveniences and

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1 discomforts and traumas associated with the breast
2 biopsy procedure: the initial discomfort,
3 inconvenience, the anxiety that is associated with
4 waiting for the biopsy to occur, and statistics or
5 publications have commented upon the trauma, even
6 though the result is a benign breast biopsy, may
7 linger for many years with that woman. Fortunately,
8 it doesn't preclude them from seeking further
9 screening, but it is a traumatic impact. There's
10 psychological trauma and physical trauma and potential
11 for complication.

12 The proliferation of literature amongst
13 radiologists and clinicians in this field discussing
14 the need to reduce breast biopsies over the last
15 decade, unfortunately, has not resulted in the
16 reduction of breast biopsies. Why? Because the
17 sensitivities remain as they are in the high eighties
18 to low nineties, and the specificities range, as I
19 stated.

20 Next slide. A patient who undergoes a
21 screening mammogram today in the patient who is
22 asymptomatic has approximately a 10 percent chance of

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1 being recalled for further diagnostic views. That
2 patient who is recalled, the patient will undergo
3 approximately 1.5 to 2 diagnostic examinations, at
4 which point the clinician or the radiologist is left
5 with the observation of whether to proceed to biopsy
6 or not.

7 We shall present to you a technology which
8 is non-invasive that in the prospective study that was
9 performed in the selected, prospective subset of
10 masses which account for nearly 50 percent of all
11 lesions that go to biopsy will show you a negative
12 predictive value approaching 100 percent, a
13 sensitivity that approaches 100 percent, and a
14 specificity that is 20 percent of women already
15 selected by all the other examinations to undergo
16 biopsy.

17 We hope by introducing a technology which
18 offers the physician and the patient a physiological
19 perspective to complement the anatomic imaging that is
20 performed by mammography, diagnostic workup, and
21 ultrasound, a chance to counsel that patient that the
22 fact that a negative predictive value in her mass may

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1 obviate the need for a biopsy.

2 Physiological imaging is likely based on
3 the exclusion or recognition of proliferative changes
4 within the breast likely due in the case of malignancy
5 for angiogenesis or the absence thereof.

6 I would like now to introduce a colleague,
7 a co-author on the paper, a principal investigator,
8 Dr. Kevin Hughes from Harvard Medical School.

9 DR. HUGHES: Good morning. As a breast
10 surgeon, I wanted to give my perspective on where this
11 machine will fit into the work of patients with a
12 breast abnormality.

13 As Dr. Parisky has pointed out,
14 mammography or other screening modalities identify
15 patients who are at risk of possibly having a cancer
16 and require additional workup. Those for whom no
17 further workup is needed go on to routine screening.
18 Those who need additional workup normally undergo an
19 ultrasound or physical exam to determine whether or
20 not this lesion is suspicious enough to require a
21 biopsy.

22 At this point in time, if the lesion is

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1 suspicious enough to require a biopsy by mammography,
2 by physical exam, or by ultrasound, our only option is
3 to go on to biopsy, either a core biopsy or open
4 biopsy, to determine whether or not this is cancer.

5 Next slide, please. How we are hoping
6 that our imaging will fit into this routine is that
7 the same patients now who have been identified as
8 being suspicious by mammography, by ultrasound, or
9 physical exam requiring biopsy, rather than going
10 directly to biopsy, will go to IR imaging as their
11 next step. If the IR imaging is negative, that
12 patient potentially could go on to followup instead of
13 a breast biopsy.

14 I think it's important to point out that
15 the IR imaging is like any other imaging modality and
16 has to be looked at in conjunction with mammography,
17 ultrasound, and physical exam. Even if IR imaging
18 comes out negative, if this is highly suspicious,
19 we'll still go on to biopsy. However, if we believe
20 that this patient is likely benign, this may help us
21 to confirm that impression and avoid a biopsy.

22 For those patients where the IR imaging is

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1 positive, these patients go on to biopsy, as
2 suggested. We are hoping that this will decrease the
3 rate of biopsy for these individuals.

4 Next slide, please. This is a case just
5 to show, again, how this will fit into clinical
6 practice. This is a patient found on screening
7 mammography to have a mass lesion in her right breast.

8 Next slide, please. Additional views on
9 ultrasound confirm this to be a solid mass lesion in
10 the breast which was not palpable.

11 Next slide, please. At this point in time
12 the patient would have been or was scheduled for a
13 breast biopsy. If the IR imaging device is approved,
14 what we then do is take the patient for IR imaging,
15 the table as you see over here and will demonstrate.
16 The patient lies flat on the table. The breast being
17 imaged fits into the hole here. The non-imaging
18 breast goes into one of these holes for patient
19 comfort. Each breast is imaged individually, and then
20 those images are combined.

21 Next slide, please. This is a look from
22 inside the table. The hole where the breast comes in

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1 is here. That hole is surrounded by six first-surface
2 mirrors which collect the heat image of the breast.
3 Those images are reflected off the reflector here into
4 the collecting camera.

5 The image that's taken of the breast are
6 these six individual mirror images made by these
7 mirrors, plus an en face image of the breast. The
8 outline of the breast itself is made in red by the
9 technician. The nipple is also marked in red by the
10 technician.

11 Next slide, please. At this point in time
12 we look at the two images of the right and left
13 breast. As you know, in this patient the lesion was
14 in the upper outer quadrant of the right breast.

15 It is important to realize that this is
16 not a visual image that can be easily interpreted by
17 a radiologist or a surgeon. Essentially, looking at
18 this area, you cannot glean any information just
19 visually. What you need is the algorithm to determine
20 whether this is, indeed, a suspicious lesion.

21 Next slide, please. At this point we
22 bring a region of interest over the area that we

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1 consider to be involved by the mammographic lesion.
2 Trying to get the lesion placed as perfectly as
3 possible is important, but not critical. Within a
4 short distance of the lesion appears to be adequate.

5 Once we identify the region of interest,
6 the machine runs through its algorithm and gives us a
7 report, which comes up as either negative or positive,
8 shown here.

9 Next slide, please. Here, again, shown as
10 a negative report. So, basically, we have a lesion on
11 a mammography we believe is benign, but we require a
12 biopsy under current clinical practice, even though we
13 all suspect this to be a benign lesion.

14 We undertake this test, which shows that
15 it does not light up in the way that we would consider
16 malignancy from the thermal imaging. This should give
17 us enough information to help us avoid a biopsy in
18 this individual.

19 Next slide, please. In this particular
20 case, under this study, we did proceed with biopsy of
21 all these patients, and this patient, indeed, had a
22 benign lesion showing periductal and stromal fibrosis.

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1 At this point I'll turn the podium over to
2 Lynn Satterthwaite. Thank you.

3 MR. SATTERTHWAITE: Good morning.

4 The first slide here shows the
5 electromagnetic spectrum. Because sensing infrared
6 energy is so central to our device success, I show the
7 infrared light as part of that spectrum. You can see
8 there that it is shorter than the radio waves we
9 listen to and longer than the x-rays that are part of
10 mammography and imaging sessions.

11 Next slide. Infrared energy is emitted by
12 the body as a result of the physiologic processes that
13 take place in the body. Our camera passively senses
14 that infrared energy and records that information as
15 temperatures. Therefore, we do no harm to the
16 patient. This is a non-invasive device. There is no
17 risk involved in sensing infrared energy given off by
18 the body.

19 What we're going to do for a few minutes
20 is to discuss the device. There are two primary
21 functions, the acquisition of the data and then the
22 evaluation of the data. We'll first talk about the

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1 device itself -- let's back up, please -- the device
2 itself, which we have a model, actually a working
3 model, over here, a working device. Then the
4 evaluation system I don't have here, but is very
5 similar to a simple desktop computer.

6 Next slide. Here I show the functions
7 that are performed during the imaging session in
8 sequence. We'll first talk about data acquisition.
9 Those that are outlined in green are those functions,
10 and we'll discuss those first today.

11 Next slide. Let me just direct your
12 attention for a minute over here to the bed. You've
13 seen a picture of the bed. The bed is composed of a
14 support unit. There's a table-top unit here. Inside
15 the bed is an optical system. Dr. Hughes gave a
16 fairly good explanation of that optical system. Also
17 inside the bed is a camera and then a simple cooling
18 system.

19 This bed functionally is equivalent to
20 what was used in the clinical trials. It is exactly
21 functionally equivalent, except that some of the
22 functions that were operated manually by the

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1 technologist are now done automated by the computer.

2 Let me just take a minute and take you
3 through the sequence here. Once the patient has been
4 enrolled or it is decided that this image is going to
5 be taken, the patient will disrobe and equilibrate.

6 We then bring the patient here. The
7 technologist will lay the patient prone on the bed.
8 You noted on the pictures on the screen -- you won't
9 see it very well here, but we'll invite you to step up
10 here and take a closer look anytime in the breaks --
11 there are three holes. The center hole is the imaging
12 hole. The two holes on the side will accommodate the
13 other breast while imaging takes place.

14 So the patient lays prone on the bed. We
15 suspend the breast pendulously in the center. This
16 center hole is where those six mirrors surround the
17 breast tissue for that imaging session.

18 The computer controls the beginning of
19 imaging. That's initiated by the technologist once
20 they note that the patient is properly positioned.
21 The imaging begins, and then 30 seconds into the
22 process the computer controls the turn-on of the

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1 cooling process, and the cooling continues as the
2 camera continues to record through the remainder of
3 our taking over a hundred images of the patient.

4 So there's a lot of simplicity here. We
5 have an optical system and a camera, a cooling system.
6 It's important to note that they are controlled by a
7 computer that takes the human element out of that.

8 I also have here a model that I'll invite
9 you to come over and take a look at. This is the old
10 "a picture is worth a thousand words" approach. But
11 this model has a miniature set of six mirrors at the
12 top.

13 Let's go to the next slide. Those six
14 mirrors that you see on the left of your screen up
15 there are first-surface gold-coat mirrors. They're
16 arranged so as to optimally image the suspended
17 breast. They're at the top of this device.

18 That information is reflected off a main
19 bounce mirror that is down here at the bottom. That
20 bounce mirror then is viewed by the camera, and all
21 the information of the bounce mirror is what's
22 recorded.

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1 On the device here is a plastic model of
2 a breast, and when you take a look here, you will be
3 able to see how we are able to see all sides of the
4 breast through the optical subsystem that is available
5 here.

6 When the imaging is complete, the
7 technologist will see two composite images similar to
8 what you see here.

9 Next slide. The camera that's central to
10 this process is a scanning camera. It uses a mercury-
11 cadmium-telluride sensor that's sensitive in the 8- to
12 12-micron band.

13 Next slide. What I show here is the
14 electromagnetic spectrum in the IR band, noted here on
15 the bottom in microns from 3 to 13 microns. The
16 arrows represent the emission of the human body of IR
17 energy. Note that the optimum emission is at about 10
18 microns, though the body emits at several wavelengths
19 here, as you can see.

20 Our camera is sensitive in the 8- to 12-
21 micron band, so you can see what we have done is
22 optimize the recording of the optimum signal given off

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1 by the body. Other sensors that have been used in the
2 past will pick up infrared energy, obviously, but it
3 won't be optimum.

4 Next slide. The camera then is important
5 because it will detect differences in temperature as
6 low as a tenth of a degree between two pixels.
7 Translated into the human breast, between two points
8 on the breast, we can see differences that are very
9 small in temperature. Our camera resolves the area of
10 the breast down to less than 2 millimeters, and it
11 takes just about a millimeter-and-a-half as the
12 smallest area that's resolvable, where you can see a
13 different temperature on the skin.

14 So with the technology we've talked about,
15 the sensitivity and the IR band, the resolution of the
16 camera, and the temperature sensitivity of the camera,
17 we're able to capture the infrared energy that's
18 emitted by the body in the form of temperatures, and
19 that provides physiological information that will
20 supplement the anatomical view provided by x-rays.

21 Because the cooling challenge is
22 important, so important, to the information that we

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1 gather with the system, I would like to just talk you
2 through that cooling challenge.

3 Next slide. First, the technologist will
4 position the patient. I show a timescale here on the
5 bottom. Once the patient is positioned, the camera
6 begins the imaging session, which continues for over
7 three minutes.

8 About 30 seconds into that imaging
9 session, the computer turns on the cooling, and that
10 cooling continues through the remainder of the little
11 over three-minute imaging session, where we take 103
12 images.

13 It is important here to note that it's the
14 computer that's doing the control there. It is also
15 important to note that, because we have a computer in
16 the system, we're accurate and precise. The cooling
17 challenge elicits that physiological challenge, and
18 then we record that view in the camera and provide
19 that to supplement the anatomical view that's provided
20 by mammographic x-ray.

21 This is an image. We're going to attempt
22 here to show you what happens during that cooling

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1 challenge. So we're going to compress about three-
2 and-a-half minutes into a few seconds here.

3 Notice the central image there, the en
4 face image, it's here in the center. The six mirrors
5 that Dr. Hughes discussed earlier present those parts
6 of the breast tissue. Then, on command, you will see
7 that light areas are warmer; dark areas are cooler.
8 During the cooling challenge you see what happens
9 there. Let's try it one more time.

10 Notice how it gets cooler as time goes on.
11 Again, we have compressed three-and-a-half, a little
12 over three minutes into a few seconds here, but you
13 get the idea of what is happening.

14 It is important to point out, again, that
15 there's no diagnostic information when the physician
16 views one of these images. This is an analysis-
17 intensive modality.

18 Next. Once captured, the infrared data is
19 processed and we develop a single, composite image.

20 Now I would like to take you through the
21 second part of this. The process for our system is to
22 evaluate the data. It is outlined in the functions on

1 the bottom here in green letters.

2 Initially, the technologist places
3 outlines on the breast. You can see here that the
4 outlines have been placed. Basically, the
5 technologist has a number of ellipses there that they
6 can move around and just capture breast tissue. The
7 physician then confirms and changes those outlines as
8 necessary.

9 Once those outlines are placed, then the
10 physician, utilizing mammographic x-ray views, will
11 localize using those x-ray views and transfer that
12 localization onto the composite image here. You can
13 see here a region-of-interest marker is placed on the
14 breast in the appropriate location.

15 Because we recognize that between
16 modalities placing the ROI may have some variance, our
17 system does a search to improve that localization.
18 What I show here is this breast tissue area here has
19 been blown up here or magnified, and that region-of-
20 interest marker is the center of this circle here.
21 What we do is calculate the pixels inside this outline
22 and take about one-twelfth of that area and surround

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1 it around this region-of-interest marker and do the
2 calculations then to potentially improve that
3 localization. We look for a stronger IR signal.

4 So we gather over 8 million temperature
5 datapoints, and then analyze select datapoints in
6 order to come up with our diagnostic information.
7 Again, it is important to point out that the infrared
8 images are not visually interpreted. This is an
9 analysis-intensive approach.

10 We then go on and do the index-of-
11 suspicion calculation. This is what is presented to
12 the physician.

13 Next. Once the region of interest has
14 been placed, it takes less than three seconds for the
15 calculation to take place, and then we present the
16 results shown here, a negative result. We actually do
17 have an index of suspicion. Here this is the version
18 of the system at this time, and we anticipate then
19 taking out this index of suspicion and just presenting
20 a test result that is either negative or positive.

21 Next. CTI provides training to both the
22 technologist and the physician for those things that

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1 are important to the success of the use of our device.
2 The technologist is trained to position the patient to
3 do the proper procedure. The technologist is prompted
4 by the computer to do certain things as far as
5 positioning and looking for artifacts that might
6 render the image not useful, and then would prompt
7 them to go back and re-image, if necessary. Then we
8 teach them about outlining the breast and then some
9 about upkeep and maintenance that is done by the
10 technologist.

11 Next. The physician, we train the
12 physician in lesion localization, particularly how to
13 translate from the x-ray view that they already are
14 familiar with onto our composite image the placement
15 of that ROI marker, and then the utilization of the IR
16 test result.

17 In summary, our system performs a
18 computerized analysis to differentiate between
19 malignant and benign tissue. It is comprised of non-
20 invasive, safe components. There's no exposure of
21 risk to the patient. It is designed to be a non-
22 invasive, adjunctive medical device for use by the

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1 radiologist.

2 I now would like to introduce Dr. Karleen
3 Callahan, who is Director of Clinical Studies.

4 DR. CALLAHAN: Good morning. I'll go
5 through the clinical study protocol, talking about the
6 study objectives, hypothesis, study design and
7 procedures, as well as the study flow, our subject
8 enrollment demographics, safety results, and then,
9 finally, our efficacy groups and statistical analyses.

10 The study objective, as stated in the
11 protocol, was then to determine whether the CTI BS
12 2100, when used in conjunction with mammography,
13 increases the ability of physicians to differentiate
14 benign from malignant breast abnormalities.

15 The hypothesis, therefore, was that this
16 differentiation between benign breast lesions from
17 malignant breast lesions was based on the relatively
18 lower strength of the infrared signal in benign
19 tissue. The goal, then, therefore, is to reduce the
20 number of benign biopsies.

21 The study was designed as a blinded
22 investigation. The initial protocol involved one site

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1 and 600 subjects. It was eventually expanded to five
2 sites in order to obtain a sufficient number of
3 malignancy for analysis purposes.

4 Our effectiveness evaluation criteria, as
5 outlined in the original study protocol, were area
6 under the curve, sensitivity, specificity, as well as
7 subpopulation analyses.

8 Our clinical sites are listed here and
9 were throughout the country: Dr. Parisky, who you
10 have already heard from, at USC, and Dr. Hughes, who
11 is in Lahey Clinic outside of Boston. We also had
12 investigators, Dr. Robert Hamm here in Washington,
13 D.C., at Providence Hospital; Dr. Esserman at Mt.
14 Sinai Medical Center in Miami, and Dr. Sardi at St.
15 Agnes Health Care in Baltimore. So we had wide
16 geographical representation.

17 The study flow was such that subjects were
18 identified and enrolled. They underwent infrared
19 imaging and then proceeded to biopsy. The biopsy
20 results, a pathology was sent to an independent
21 research organization, Quintiles, and kept vaulted
22 from CTI.

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1 The IR imaging data as well as patient
2 information obtained in a case report form and
3 mammography were sent to CTI. A trial read was done
4 by independent evaluators, as I'll discuss
5 subsequently.

6 After the trial read was completed and the
7 database controlled and locked, at that time the
8 pathology results then were unblinded and sent to CTI
9 and Battelle for analysis purposes.

10 Our evaluator panel for the infrared
11 procedure were seven independent mammographers who are
12 currently practicing. Three of these mammographers
13 were director of their breast imaging centers; one had
14 participated in MQSA standards development. They were
15 all currently practicing and read several thousand
16 mammograms each year. Again, they were independent
17 from the sites and blinded to lesion pathology
18 results.

19 The clinical research organization that
20 was involved in this study is Quintiles. They
21 monitored the investigative sites, did 100 percent
22 source documentation. They held the blinded pathology

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1 results and, again, after the IR evaluation phase, a
2 locked database was supplied to them prior to
3 unblinding.

4 I'll next go over the study
5 inclusion/exclusion criteria. The study inclusion in
6 the original protocol was subjects that were
7 recommended for biopsy based on mammography and/or
8 clinical findings. These subjects did receive and
9 sign IRB-approved informed consents.

10 Exclusion criteria were subjects that had
11 previous breast surgery. I will give a little bit
12 more details in a moment. Other exclusion is if they
13 had had radiation in the breast that was to undergo
14 biopsy, if they had had either breast implants or
15 breast reduction surgery. There was a weight
16 limitation of 300 pounds, based on the table weight
17 limit. Other exclusions were patients that were
18 pregnant or had previous diagnosis of breast cancer.

19 For the study protocol, there were two
20 amendments during the study trial period. The first
21 amendment was in November of 1998, and this amendment
22 changed the method of evaluating the mammogram and IR

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1 imaging.

2 The original protocol had intended that
3 the site investigator that enrolled the patient would,
4 in fact, assign mammographic LOS, level of suspicion,
5 similar to BIRADS categorization, as well as do the IR
6 imaging evaluation. It was determined in this
7 amendment that, in fact, these reference independent
8 radiologists would do that procedure. I will talk a
9 little bit more about some of the developmental
10 problems with this independent evaluation, trying to
11 determine level of suspicion from mammograms.

12 The second protocol amendment was
13 initiated in June of 1999, and it reduced the prior
14 breast exclusion criteria. There initially had been
15 no prior breast surgery for three years; that was
16 reduced to a one-year time period.

17 So to reiterate, the investigators would
18 screen, the principal investigators would screen and
19 enroll subjects. The IR data acquisition would begin
20 at those sites, and the original investigator would
21 record a variety of subject data, including lesion
22 descriptor; that is, was this a mass,

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1 microcalcification, architectural distortion, and so
2 forth? They would describe the lesion size and they
3 would complete the pathology outcome.

4 The reference or the evaluating
5 radiologist would do a level-of-suspicious
6 determination, and when they was done, this was based,
7 then, on radiology reports and overread of the
8 mammography films that had been provided by the
9 original investigative site.

10 It became apparent that there were some
11 issues related to this because it was not being done
12 in real time. These reference radiologists did not
13 always have all the information that would have been
14 available to the original investigator; that is, they
15 wouldn't have had prior films, and oftentimes a
16 radiology report might contain additional information,
17 for example, ultrasound information.

18 So a comparison based directly on
19 mammography alone was difficult to establish. Because
20 of this, we eventually decided that comparison for
21 efficacy to the biopsy decision -- that is, these
22 patients went to biopsy; we had the pathology result

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1 ground truth that this comparison was more rigorous.

2 Our study procedures for the physician
3 evaluators then were that they reviewed the mammogram.
4 They checked the breast outline, as you have heard.
5 They placed the ROI marker on the IR image, and then
6 an assignment of either a negative or positive IR
7 result was obtained.

8 I will discuss the subject enrollment
9 briefly. This shows it across our five sites. Our
10 total patient enrollment for the study was 2,407
11 patients, and our enrolling centers ranged from 170 up
12 to over 800 patients.

13 You will hear some of the additional
14 demographics later on from the FDA. So I will just
15 talk about lesion size.

16 The majority of lesions were either
17 between -- and this is in our final efficacy group
18 that I'm referring to here of 490 masses -- our lesion
19 size ranged between .5 and 1 centimeter or greater
20 than 1 sonometer. There were a small number of masses
21 less than .5 sonometers.

22 For safety issues, of the 2,400 subjects

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1 enrolled, all were followed for safety. There were
2 four adverse events noted. Two of these were mild and
3 felt related to the device and related to discomfort
4 lying on the imaging bed or just exacerbation of a
5 previous condition. Two other adverse events not
6 related to the device were also reported.

7 I am going to spend a little bit of time
8 about the withdrawn cases for study flow. So I will
9 go through a series of charts here.

10 We started out with, as I just mentioned,
11 2,407 subjects. Seven hundred of those were in an
12 algorithm development group and 275 were not part of
13 the original unvaulting. So when we began the
14 analysis phase, we had 1,432 subjects that had some
15 with multiple lesions. So we had 1,660 lesions.

16 There were three categories of withdrawn
17 cases that were determined prior to the evaluation
18 phase. The first group were those that we're calling
19 non-conformatory to study protocol. Basically, these
20 were patients that did not undergo biopsy, and the
21 flow of the study was such that patients were -- these
22 were often referral centers -- patients had been

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1 recommended for biopsy. They came in, and perhaps
2 they were scheduled for an ultrasound, not a biopsy,
3 and a cyst, fluid-filled cyst, was identified and they
4 did not proceed to biopsy. So there were a number of
5 cases that did not undergo biopsy. Of course, they
6 were dropped.

7 There were also cases where we had missing
8 or incomplete mammography films. That is, if there
9 weren't sufficient views for our independent
10 evaluators to localize, then they could not be entered
11 into the evaluation phase.

12 Finally, there were some cases with
13 unusable infrared images. A lot of those difficulties
14 were related to cooling, the start of cooling, which
15 wasn't automated at the time of our clinical trial, as
16 well as positioning issues. With technologist
17 training, we think that we have mitigated, attenuated
18 that problem. So at this point we had withdrawn
19 cases. This was determined prospectively prior to
20 entering the evaluation phase.

21 Those subjects that did go on to the
22 evaluation phase, there were also a few more withdrawn

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1 do statistical analysis comparing those withdrawn
2 lesions to those that were analyzed. This says no
3 statistically-significant differences were found. One
4 difference was that more of the spiculated masses were
5 evaluated, and probably Dr. Rust will address that.

6 So our mass, when we did all the cases, we
7 also then decided to look at the masses and focus on
8 masses, because to minimize the risk to patients,
9 maximize benefit for labeling and patient benefit
10 purposes, it was felt that our target population would
11 focus on masses.

12 The FDA did request a confirmatory study
13 for masses, and we did another small confirmatory
14 study with those 275 cases that remain vaulted looking
15 at the masses. So our efficacy groups that Dr.
16 Parisky will describe include our original study with
17 all lesion types, those of masses from the original
18 group, a confirmatory study, and then our combined
19 results.

20 So our confirmatory study involved those
21 275 patients. They underwent the identical evaluation
22 process, and the result was 78 masses.

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1 cases, primarily because the physician evaluator could
2 not evaluate the case. This could be due to, for
3 example, if they did not see a lesion in the area that
4 had been described on the case report form or the
5 lesion didn't correspond with the descriptor.

6 There were a few also that were location
7 discrepancies; that is, a priori we made a
8 determination model for, if the ROI marker was
9 significantly outside of the location of the biopsy
10 lesion as described in the case report form, it was
11 removed from the analysis phase. Again, all these
12 withdrawn cases were determined prospectively prior to
13 unblinding of our results.

14 Finally, then, for our original study, we
15 described 875 lesions in 769 subjects. We had, as you
16 will hear from Dr. Parisky subsequently, we had good
17 results with all the lesions. However, we also looked
18 at a subset we had described that we would do
19 prospectively, and that is the masses.

20 So the points I wanted to make were that
21 the lesions withdrawn were done prior to IR evaluation
22 or after IR evaluation prior to unblinding, and we did

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1 types that were prospectively stated; that is, masses,
2 calcifications, and distortions. So we have listed on
3 this slide the seven possible target populations that
4 could have resulted from the analysis.

5 Next slide, please. Now given that we
6 could be here before you today reporting on one of
7 seven possible target populations, and we are, in
8 fact, proposing that the device be targeted for the
9 subset for which the best performance was obtained, it
10 is necessary to carefully handle the statistical
11 analysis.

12 There are two options for handling this
13 situation. One would be to perform an entirely new
14 study and draw your statistical conclusions only from
15 the new study data.

16 Another option is to apply a correction
17 that validates the statistical conclusions drawn from
18 the original study data. Either approach is
19 scientifically correct, and I should also point out
20 that it is possible to apply a combination of the two
21 approaches, which is in fact what CTI did.

22 As Dr. Callahan pointed out, a

1 confirmatory study was carried out using a subset of
2 78 masses from the 275 patients that remained
3 unvaulted at the time that the target population was
4 focused on masses, and that data from the new
5 confirmatory study was added to the clinical trial
6 dataset.

7 A Bonferroni correction then was applied
8 to the results for the combined data from the original
9 study and the confirmatory study to correct the
10 statistical inferences for the fact that seven
11 potential target populations were considered
12 prospectively. Now when I say -- could you back up,
13 please? -- when I say, "conservatively applied," I
14 want to point out that no credit was taken for the
15 fact that the data from the confirmatory study is
16 actually new and independent data. So the Bonferroni
17 correction was simply applied to all of the data,
18 taking no credit for new data.

19 The result is that statistical conclusions
20 that we would report for any of the seven possible
21 target populations are valid, and, therefore, the
22 conclusions we're reporting for the target population,

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1 the masses, are, therefore, valid.

2 Okay, next slide. The result is that, if
3 you simply apply direct statistical procedures to the
4 data and calculate confidence intervals for
5 sensitivity and specificity with no correction, you
6 get a confidence interval for sensitivity going from
7 95.6 to 100 percent and for specificity from 16
8 percent to 22.8 percent.

9 Applying the correction that corrects for
10 the fact that we're here reporting on the best of
11 seven target populations, the correction essentially
12 widens the confidence intervals to make them valid,
13 and the confidence interval for sensitivity now
14 becomes 93.5 to 100 and for specificity 14.5 percent
15 to 24.6 percent.

16 Thank you. I would like to now turn it
17 back over to Dr. Parisky.

18 DR. PARISKY: I am remiss in the fact that
19 I forgot to mention my financial disclosures, of which
20 I have none. I am principal investigator. I do serve
21 as a consultant to the company. I have no equity in
22 CTI. I apologize for that.

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1 I will now share with you the efficacy
2 results from the original trial and then the subset
3 and confirmatory trials.

4 These are the numbers which I will speak
5 about. First, the original trial, looking at all
6 subgroups.

7 Next. Of the 875 lesions studied, and
8 these are again, I remind you, prospectively-chosen
9 patients who by mammographic and clinical criteria
10 were destined for biopsy and then studied, there was
11 a 14 percent specificity, 96 of the 688 benign
12 lesions. Lesions including descriptors such as mass,
13 microcalcifications, architectural distortion were
14 assigned a negative IR result.

15 Next. Interestingly, though, there was a
16 97 percent sensitivity. Of the 187 malignant lesions
17 that were in this original population, including
18 masses and calcifications, 180 were correctly assigned
19 a positive IR result; seven received a falsely-
20 assigned negative IR result.

21 I would like to draw the Panel's
22 attention, and especially the mammographers and those

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1 who clinically practice in the field of breast
2 treatment or breast surgery or breast diagnosis. So
3 let's look at the false negatives.

4 The population were that of
5 microcalcifications. That was the descriptor. The
6 pathology was four DCISEs, two DCISEs with focal
7 microinvasion and only one intraductal and
8 infiltrating ductal carcinoma that was described as
9 calcifications rather than mass. I was impressed by
10 this, that there were no invasive malignancies
11 described as mass in the false negative.

12 When we looked at masses alone within the
13 original study group, this target population which was
14 prospectively selected or targeted, and looking
15 specifically at masses, we increased our specificity
16 to 18 percent.

17 Next. We rendered 100 percent
18 sensitivity. Of the 90 malignant masses within this
19 population group, there was no false negative
20 assigned.

21 The confirmatory study, as Dr. Callahan
22 explained, the 78 patients or 78 masses in the 200-

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1 and-some-odd patient groups in this confirmatory set
2 of 78 masses, specificity increased was 25 percent.
3 Sensitivity was reduced. Of the 15 malignancies, 14
4 were correctly assigned a positive IR result and one
5 was incorrectly assigned a negative result. Let's
6 take a second to pause and take a look at what that
7 cancer was.

8 That cancer, as pathologically evaluated,
9 including basement membrane standing, was DCIS, a non-
10 invasive malignancy presenting as a mass, which those
11 of us who practice radiology know that occurs
12 approximately 3 to 7 percent of the time, presentation
13 of DCIS.

14 If we combine these two groups, the
15 combination yielded a specificity of 19 percent and a
16 sensitivity of 99 percent. Again, the one incorrectly
17 or falsely-negative cancer was a non-invasive
18 malignancy.

19 Next. This is a distribution of the
20 lesions that were identified as malignant masses. We
21 had both invasive and some non-invasive masses,
22 reasonable distribution.

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1 Go to the next one. Benign masses
2 accounted, fibrocystic disease but not cysts. These
3 are fibrocystic disease, primarily fibrosis and
4 microcysts, fibroadenomas and a host of others,
5 including fibrous mastopathy and the spectrum of
6 benign etiologies that pathologists are confronted
7 with.

8 Next. So we step back and take a look and
9 see what is the intended population of this device.
10 Again, I remind you that well over 1.3 million women
11 are biopsied annually. A fair percentage of those are
12 for the subgroup masses.

13 When a radiologist today is confronted
14 with a mass observed on the mammogram, they are
15 offered several tools, diagnostic mammography and
16 ultrasound being primary. Much more expensive
17 modalities such as Sestamibi, MRI, and PET scan have
18 been proffered. There's published sensitivities and
19 predictive values I don't believe approach what we
20 have presented here.

21 This is a tool that would be used to
22 provide information, as Dr. Hughes stated, that the

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1 radiologist looks at a mass. He or she performs an
2 ultrasound, and they get a feeling and there's a
3 perspective on whether or not to send this patient to
4 biopsy. Those are based on anatomic criteria. So
5 far, physiologic imaging, including Doppler
6 ultrasound, have not provided a very good indicator or
7 a good indicator for whether to proceed with biopsy or
8 not.

9 This is a tool that appears to measure
10 physiological changes like these related to blood flow
11 in the region. I think the data supports use of this
12 in masses. I hope the Panel and members of the
13 audience are somewhat excited about the fact that we
14 -- with the DCIS. I think that eventually we'll
15 stratify some of that DCIS and look at the low grade
16 and high grade, because we're now looking at the
17 physiology. We're looking at the innerworkings of the
18 breast in a rather inexpensive and non-invasive way.

19 We will use this to counsel our patients
20 to say: You have a mass. Ultrasound tells me it's
21 solid. Another examination tells me that, with a very
22 high, near absolute negative predictive value, we

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1 could obviate the need for biopsy or we need to
2 proceed to biopsy. It is a piece of reassurance to
3 both the doctor and to the patient.

4 Mind you that the numbers I showed you,
5 these specificity, that was superimposed on patients
6 who were already mammographically-determined to
7 proceed to biopsy.

8 Next. I think I have discussed intended
9 population as masses. Continue.

10 In the schematic I'll reintroduce: The
11 patient is seen. The mammogram says that it requires
12 a further workup. The lesion is characterized as a
13 mass. At that point in time, or in conjunction, in
14 parallel to ultrasound, as part of the diagnostic
15 workup, a new tool is now available which will allow
16 the physician to determine, based on the results of
17 positive or negative, whether or not to consider
18 biopsy or to consider short-term followup, as is
19 pretty standard in clinical practice today, without
20 the additional physiological test.

21 Next. We avoided biopsy in 74 benign
22 masses in a little over 380 patients. At risk was

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1 delaying one biopsy of a non-invasive malignant mass
2 in over 100 malignancies.

3 I would like to thank the Panel for its
4 consideration. Thank you.

5 I would like to now reintroduce Dr. Rust.

6 DR. RUST: What I would like to do is end
7 the presentation of technical material as part of the
8 sponsor presentation by putting the performance
9 results that Dr. Parisky presented in perspective in
10 terms of their effect on the health care system.

11 This 2x2 table simply takes the
12 performance data that Dr. Parisky presented and puts
13 it in the form of a 2x2 table where a true pathology
14 is indicated in one dimension and the results of the
15 IR test are indicated in the other direction.

16 Of course, in the trial lesions with a
17 negative IR result did receive a biopsy because that
18 is what is required by current practice. However, if
19 you interpret these results, what this implies is that
20 these 74 lesions for which there was a negative IR
21 result would not have gone to biopsy and, therefore,
22 74 benign biopsies would have been prevented.

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1 Again, this one lesion did receive a
2 biopsy in the trial, but the implication is that this
3 one lesion would have been a cancer for which
4 diagnosis would have been delayed.

5 Now to take these performance results and
6 put them in perspective in terms of effects on the
7 health care system, what I'm going to do is basically
8 extrapolate them up to the annual population to which
9 this device could be applied. The way I am going to
10 do that is to start with the 1.3 million biopsy figure
11 that Dr. Parisky mentioned earlier and apply a 45.5
12 percent factor to determine the number of masses
13 biopsied annually. That is where the 591,500 total
14 mass biopsy figure comes from.

15 The 45.5 percent figure that I apply is
16 simply what we observed in the clinical trial. All of
17 the other numbers in the table simply follow by
18 extrapolating up from the table on the previous slide
19 to this 591,500 number.

20 The impact is that in practice we would
21 expect to prevent approximately 90,000 benign mass
22 biopsies annually in the U.S. if the device was

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1 applied to the entire population to which it is
2 intended, and 1,207 malignant masses would have a
3 delayed diagnosis.

4 Next slide, please. Now if you
5 incorporate cost information into this picture to do
6 a cost/benefit analysis, in the way of costs you first
7 have to consider the cost of the IR procedure. We
8 are, in fact, adding cost into the health care system.
9 At a median level of the procedural cost of \$225, we
10 are, in fact, adding 591,500 new procedures into the
11 system at a cost of \$133 million. Another cost is
12 that 1,207 cancers would have a delayed diagnosis.

13 Now the benefits of the device would be
14 that approximately 90,000 benign biopsies would be
15 prevented at an average cost of \$3,000 per biopsy,
16 resulting in \$268 million of cost removed from the
17 health care system, and the negative effects of 90,000
18 benign biopsies would also be mitigated.

19 So in that, 1,207 cancers would receive
20 delayed diagnosis; the net cost savings to the health
21 care system would be \$135 million annually, and the
22 negative effects of approximately 90,000 benign

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1 biopsies would be mitigated.

2 I should point out that the \$225 figure
3 that I used for the IR procedure is the midpoint of an
4 anticipated range for the procedure of \$150 to \$300.
5 If you apply that entire range, this net health care
6 cost savings actually ranges between \$90 million and
7 \$179 million, depending on the cost of the IR
8 procedure.

9 So now I would like to turn this over to
10 Lynn to basically summarize our presentation.

11 MR. SATTERTHWAITTE: I'll apologize;
12 hopefully, John Brenna is just not feeling well
13 temporarily here. I'll try to finish up in his place.

14 Our proposed indication is that we are
15 intended for use as an adjunct to mammography, to
16 safely avoid biopsy of benign breast masses that would
17 otherwise have gone to biopsy.

18 Next. We're recommended for all patients
19 receiving a negative IR test result be similar to the
20 recommendation for care of mass that is assigned a
21 mammographic BIRADS category 3.

22 Next. We want to take a minute and just

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1 briefly go through the history of our interaction with
2 the FDA. We have enjoyed a great relationship with
3 the FDA people in counseling us, coaching us,
4 reviewing, and so on.

5 Our original submission was done in June
6 of 2001. We have talked about our movement to a
7 subset of masses which we presented to the FDA in the
8 form of an amendment in February of 2002, where they
9 indicated to us there were things that we needed to do
10 to confirm that data. We worked with the FDA
11 personnel to come up with a plan to utilize the 275
12 patients for which the pathology was still vaulted to
13 do a confirmatory study using that set of patients,
14 which had the 78 masses we have talked about.

15 The FDA folks, reviewers, indicated that
16 they were fine with our plan. We moved ahead to
17 evaluate and analyze those patients and provided the
18 results of that analysis in Amendment 5. That is what
19 we call "Confirmatory Study Results" there.

20 We have had site audits by the Office of
21 Compliance. We've had a sponsor audit by the Office
22 of Compliance, and by all measures we think we

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1 successfully completed those audits.

2 We have been invited to a panel in July of
3 this year, and then subsequent to that invitation, in
4 working with the FDA, we mutually agreed to postpone
5 the date for this meeting for administrative and
6 logistical reasons.

7 Next. So somewhat in a conclusion manner
8 here, the original study protocol was developed with
9 the FDA. A confirmatory study plan to deal with the
10 confirmation of the subset of masses was reviewed and
11 approved by the FDA. That did target, formalized our
12 targeting of masses or lesions with mass as a
13 descriptor. Those results were combined with original
14 study results. On review of those results, the FDA
15 scheduled this Panel meeting.

16 In summary, let me just recap here. We
17 have a device that is non-invasive. It's safe,
18 painless, to be adjunctive to mammography x-ray. It
19 complements the anatomical view with the physiological
20 view.

21 Our clinical study performance is an
22 improvement over the biopsy decision. Nineteen

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1 percent specificity we think is significant. We
2 believe that it has the potential to reduce health
3 care costs. We believe that we have demonstrated that
4 we are safe and effective medical device for the
5 proposed indication for use.

6 I ask that you recommend approval of our
7 device as you complete your review. Thank you very
8 much.

9 CHAIRMAN MEHTA: We would like to thank
10 the sponsor for their presentation. At this point, if
11 there are questions from the Panel specifically in
12 terms of clarifications only -- we'll have discussion
13 questions later on in the afternoon -- but if there
14 are clarification questions from any of the Panel
15 members, this would be a good time to ask the sponsor
16 for that.

17 DR. TOLEDANO: The first one is, looking
18 at your table, I am reminded that in many mammographic
19 procedures women with large breasts require multiple
20 images. How well do you accommodate women with large
21 breasts on your table?

22 DR. CALLAHAN: I'm not aware in our

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1 clinical trial that we had any sort of dropout because
2 of non-accommodation of size. Perhaps Dr. Hughes or
3 Dr. Parisky could comment. So I am not aware that
4 that has been a problem.

5 DR. TOLEDANO: Okay.

6 CHAIRMAN MEHTA: I do have a question. I
7 was somewhat confused about the specific indication
8 that is being sought in terms of the BIRADS category.
9 In the earlier presentation by Dr. Hughes, he
10 indicated that, using this nice flow diagram, what one
11 would do is perform a physical exam, mammography,
12 ultrasound if necessary. If there's a highly-
13 suspicious lesion -- i.e., a BIRADS category, say for
14 example, of 5 -- one would still go ahead and do the
15 IR imaging. Then if the IR imaging is negative, you
16 would still go and do the biopsy, because, obviously,
17 the clinical information suggested that this was a
18 highly-suspicious lesion.

19 But I think one of the final cites
20 suggested that the BIRADS category would be restricted
21 to 3. Can you clarify for us whether there is a
22 specific BIRADS category you are asking for in this or

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1 not?

2 DR. HUGHES: I believe it's for BIRADS 4
3 and 5. I believe what the slide was trying to say was
4 that we might be able to take a 4 or 5, which is where
5 the test would be done, and then downgrade it to a 3;
6 whereas, rather than or instead of doing a biopsy on
7 a 4 or 5, we would call it a 3 and do a followup. So
8 we are not looking for BIRADS 3 at all. BIRADS 4 or
9 5. Is that accurate, Lynn?

10 DR. CALLAHAN: Well, I would say that
11 that's fairly accurate, but we're not restricting it
12 to a BIRADS categorization. The decision is, if this
13 is a patient that the physician feels a biopsy might
14 be warranted, then the IR procedure would be an
15 alternative or an adjunctive test.

16 For example, we know that there are BIRADS
17 3s that the ACR recommendation is six-month followup,
18 but for reasons, either personal reasons of the
19 patient or the physician, oftentimes these patients do
20 not desire for that six-month followup. So in that
21 sort of situation this procedure would be appropriate,
22 we believe.

1 CHAIRMAN MEHTA: I'm sorry for my
2 confusion, but three or four slides into the last
3 presentation there was a statement about a BIRADS
4 category. Can you put that slide back up again?
5 There you go. Can you clarify this slide for us?

6 DR. CALLAHAN: This statement refers to
7 what would be the labeling indication for a negative
8 IR result; that is, a negative IR result, the
9 recommendation would be that the followup be six-month
10 followup, similar to a BIRADS 3. So I am sorry for
11 that confusion.

12 DR. CONANT: I have a quick question, I
13 hope quick.

14 I'm not sure I completely understand the
15 flow, the clinical flow, accrual. The level of
16 suspicion that then would prompt one to biopsy or not
17 is based purely on the mammography or the combination
18 of the mammography and ultrasounds?

19 Because, for example, one case that was
20 shown, I think the clinical case of two views of the
21 breast, looked like an asymmetric density, perhaps not
22 a mass. Then if the ultrasound was negative -- I am

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1 wondering how the ultrasound plays into all of that
2 and whether the determination of mass is made by
3 ultrasound or mammography.

4 DR. CALLAHAN: For this study the
5 determination of the descriptor was supposed to be
6 based solely on mammography. It was started, was
7 initiated in 1997. Ultrasound was not part of the
8 study protocol. However, the fact is that we know
9 that standard clinical practice was utilized.

10 So that if women had something that
11 appeared to be a mass by mammography and had been
12 recommended for biopsy, they would have been enrolled
13 in our study, but then ultrasound may have been
14 performed; it was found to be a fluid-filled cyst; the
15 biopsy was cancelled. So that accounted for some of
16 our dropout.

17 So the study protocol did not specifically
18 collect the contribution or the impact of ultrasound.

19 DR. CONANT: So there would be cases where
20 a mass was considered on mammography, but the
21 ultrasound could have been negative?

22 DR. PARISKY: Correct.

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1 consideration into this trial. In some centers, in
2 talking to my colleagues, any ultrasoundographically-
3 solid mass is biopsied where in other centers
4 ultrasound is used to try to attempt to characterize
5 based on work that you know, Stavros and such, to try
6 to obviate the need for biopsy.

7 Ultrasound I believe was at least, we know
8 from reviewing the medical charts, was employed in a
9 fair percentage of these patients, but was not the
10 determinant to proceed to biopsy. At that time
11 clinical judgment by the physician in attendance
12 determined.

13 It should be noted that a number of these
14 patients who were enrolled initially was with a
15 suspect mass required for the workup, and part of the
16 large withdrawal pool was because they were enrolled
17 and, subsequently, by ultrasound to be shown to be
18 cysts.

19 I think the FDA Panel is familiar with a
20 process or subselection out like that, considering
21 that that was presented to you during one of the
22 ultrasound panels in which enrollment was made, and

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1 then a great majority of the cases were dropped from
2 consideration because cysts were discovered. So the
3 patients were enrolled based on mammographic findings.

4 DR. CONANT: But, clinically, at that
5 point one wouldn't be recommending a biopsy for the
6 inclusion criteria.

7 DR. PARISKY: A patient would be
8 considered for biopsy if they had an abnormality on
9 mammography or referred, in my instance which is a
10 referral center, would be referred for consideration
11 for a biopsy.

12 DR. CONANT: Okay, that to me would be
13 like a category zero, that ultrasound was needed.
14 That's okay; we can talk later.

15 DR. PARISKY: Yes, that's arguable as to
16 how one addresses that.

17 DR. CONANT: And were there asymmetric
18 densities? That's quite a common category in BIRADS
19 that I didn't see included.

20 DR. PARISKY: Asymmetric density, do we
21 have the numbers on asymmetric?

22 DR. CONANT: Not quite a mass, for those

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1 of you who don't use that term, it's --

2 DR. PARISKY: You know, again, it's open
3 to personal conjecture that an asymmetric density seen
4 in one view -- we did have cases that, if it could be
5 seen, if the density could be seen in two views, some
6 physicians might categorize that as a mass, having
7 been able to describe it in two views.

8 We were not particularly rigid in terms of
9 specific criteria for determination of mass and left
10 it to the individual investigators.

11 DR. CONANT: For example, two-thirds of
12 the margin's convex --

13 DR. PARISKY: No, that was --

14 DR. CONANT: -- on two views equals a mass
15 versus --

16 DR. PARISKY: That was not, those rigorous
17 criteria were not applied.

18 DR. CONANT: And the BIRADS
19 characterization was done by just one radiologist from
20 the mammogram?

21 DR. PARISKY: Again, the introduction and
22 mandate of utilization of BIRADS occurred in the midst

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1 of the trial.

2 DR. CONANT: I think 1997, is that right,
3 or 1996?

4 DR. PARISKY: No.

5 DR. CONANT: No?

6 DR. PARISKY: The rule, I think, came in
7 1999?

8 DR. CONANT: I'm not sure.

9 DR. PARISKY: April 1999 was the final
10 rule. So by mandate, that was not to be included in
11 each of the reports until 1999, so through half of the
12 reports.

13 So the difficulty with BIRADS, some
14 reports reviewed all of them; some reports included
15 BIRADS; some negligently didn't include BIRADS even
16 after the mandate date. So we attempted to have the
17 physicians in the separate pool try to develop a level
18 of suspicion, but, again, as Dr. Callahan pointed out,
19 they didn't have access to prior films; they didn't
20 have access to some of the additional imaging or the
21 films that were provided were just that of the lesion
22 and the breast in question.

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1 So that proved to be very cumbersome,
2 which is why, again, we went back to what we thought
3 was the gold standard, acknowledging the fact that
4 there is a 3 to 5 percent false negative even with the
5 gold standard.

6 DR. CONANT: The gold standard of?

7 DR. PARISKY: Being biopsy.

8 DR. CONANT: Oh, okay. Not variability
9 within readers --

10 DR. PARISKY: No.

11 DR. CONANT: -- which is quite large?

12 DR. PARISKY: Well, more so in --

13 DR. CONANT: Thirty percent.

14 DR. PARISKY: More so in DCIS than
15 invasive, and I think that that's a consideration,
16 something, hopefully, you dwell upon, given the fact
17 that we looked, you know, at the low-grade DCISes that
18 were false negatives. But in terms of invasive
19 cancer, I think the variability is much less than it
20 is in DCIS.

21 I apologize, I was acting in professional
22 capacity just now.

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