

1 of these procedures, it really is now, just in the
2 last year, that it is being offered for native
3 patients to have the reconstruction services and
4 those provisions.

5 I know that there is just not a whole lot
6 of clarity when it comes to that, in that specific
7 population.

8 DR. HARRISON: It is very cloudy, because
9 presumably, in that setting, in that clinical
10 setting, you have retained all the natural breast
11 tissue, you simply have implants placed, so that is
12 someone who clearly would need to continue to be
13 screened age specific. I am still confused.

14 MS. HARVEY: Dr. Kopans.

15 DR. KOPANS: Dan Kopans, Boston,
16 Massachusetts.

17 I just wanted to reinforce what you just
18 said, Dr. Harrison, that the standard of care is to
19 not do routine mammographic imaging of women who
20 have had mastectomies on the mastectomy side.

21 There are only two papers that I am aware
22 of looking at women who have had tram flaps, and
23 here is some debate about whether it is valuable
24 when they have had trams, but women who have
25 implants on the mastectomy side, if it has been a

1 simple mastectomy or modified radical mastectomy,
2 there are no data supporting doing mammography **of**
3 the implant side.

4 As I recall, in the discussions years ago
5 about implants, as Dr. Finder was pointing out,
6 really, the implant discussion had to do with
7 augmentation, and not reconstruction.

8 MS. HARVEY: Dr. Pisano.

9 DR. PISANO: I just want to make a comment
10 in reference to the story from California. I think
11 that was obviously, a tragic event, and horrible
12 thing for the patient, but I feel like there really
13 is a lot of guidance from professional societies
14 both for technologists and radiologists, and
15 probably physicists, too, about the imaging of
16 breast implants.

17 This particular technologist obviously
18 made an error, it sounds like to me from the story,
19 but without knowing more about it, it is hard to be
20 sure, but I don't think we should leap from one
21 story to we need stronger regulatory oversight on
22 this particular issue.

23 There is actually a fair amount of
24 information out there for technologists and
25 radiologists already **for** implants for cosmetic

1 purposes, and the same, in my opinion, goes for the
2 issue of the reconstructed breast. There is a lot
3 of information out there.

4 We teach people what Dan and Debbie have
5 already said, which is that you should not be
6 imaging these people routinely after a mastectomy.
7 It is too confusing and we find more false
8 positives than negatives, so I feel like the
9 regulatory guidance is sufficient, as written,
10 myself.

11 DR. HARRISON: Last comment. As many of
12 you know, in the situation with mastectomies, you
13 can have upwards of 5 to 6 percent of breast tissue
14 still there after mastectomy, so that imaging of
15 those areas, if there are clinical concerns, as has
16 been pointed out, is specific.

17 Very clearly, if something is palpated, if
18 there is concern about those areas, those areas can
19 be imaged, but routine imaging is not expected.

20 DR. IKEDA: I agree and I think that if
21 the patient has a problem that is a medical
22 decision and it is a physician decision with the
23 patient rather than I think something that should
24 be seen by regulatory oversight.

25 I think there is plenty about imaging the

1 breast with FDA regulations.

2 MS. HARVEY: Any more comments about that?

3 DR. FINDER: If we are finished with
4 comments about Modification Document No. 5, there
5 are some issues that have come up recently
6 referable to use of assessment categories, and I
7 just wanted to kind of bring up the issue before
8 the committee because I understand that the BIRADS
9 Committee, the people that came up with assessment
10 categories many years ago and which we have
11 basically pretty much adopted into our regulations,
12 is reviewing the current use of the assessment
13 categories.

14 I just want to bring up some issues that
15 we have become aware of referable to this.
16 Obviously, the idea behind the use of assessment
17 categories was to get some standardization into the
18 medical report, so that anybody who is reading
19 these reports would have a pretty good idea of what
20 was going on.

21 I am sure that radiologists on the panel
22 can tell you about the two- and three-, and
23 four-page reports that used to be issued, and by
24 the time you finished reading them, you didn't know
25 where you were or what anybody was trying to say.

1 In order to alleviate that problem, the
2 use of assessment categories was mandated. Right
3 now there are basically six assessment categories
4 that can be used in the reports, and my
5 understanding is, is that the BIRADS is looking at
6 some of these because we have encountered
7 situations where one of these assessment categories
8 may not apply in some of the areas that we have
9 been aware of. For example, people have raised
10 concerns about using the currently allowed
11 assessment categories when you are evaluating a
12 postoperative breast.

13 There really is no great assessment
14 category that fits that type of a situation. It is
15 kind of hard to say that a patient that has just
16 been diagnosed with breast cancer has a negative or
17 a benign looking breast when you know that they
18 have got a diagnosis of malignancy.

19 Other situations that have caused some
20 concern are dealing with the male breast. Not a
21 lot of patients get these, not a lot of male
22 patients end up getting mammography, but when they
23 do, they are also covered under the regulations,
24 and their reports also require an assessment
25 category.

1 Other areas of concern that we have heard
2 from the community deal with the use of the
3 incomplete assessment category for situations where
4 they are waiting for comparison films. Again, no
5 great way to define it in terms of the current
6 assessment categories.

7 Other issues deal with Assessment Category
8 3 are probably benign. Some people don't like the
9 recommendation that follows in BIRADS where all
10 probably benign lesions are supposed to have a
11 recommendation of follow up rather than in some
12 cases where they want to recommend biopsy.

13 Now, that is not a problem for the MQSA
14 regulations because we don't tie our
15 recommendations directly to the assessment
16 categories, but that is an issue that we keep
17 hearing about.

18 Another issue that has come up deals with
19 the possibility of using multiple assessment
20 categories. In our requirement that if you are
21 going to do that, let's say you have two or three
22 lesions on the mammogram, you have to assign an
23 overall assessment category, which is based on the
24 worst situation.

25 The theory behind that or the thinking

1 behind that was that we had situations where there
2 were multiple lesions on the mammogram, the report
3 discussed all of them. Unfortunately, they
4 discussed the benign ones first and buried the
5 malignant one in the middle of everything, and they
6 were missed.

7 So, the idea here was to require an
8 overall assessment category that was the worst one,
9 **so** that people would know not to miss the cancer.

10 Every solution creates its own problems,
11 and there is at least a theoretical possibility
12 under our system where you have to list one as the
13 overall assessment category. Let's say there is a
14 suspicious lesion and there **is** one that requires
15 additional workup and incomplete.

16 If you only have one assessment category,
17 the overall assessment category of the suspicious
18 one, is it possible that somebody will forget about
19 the other one that needs further evaluation.

20 So, these are some of the issues that we
21 have encountered. We would like the committee's
22 discussion on this a little bit, taking into
23 account that the **BIRADS** group is looking at
24 modifying their assessment categories to deal with
25 some **of** these issues.

1 **DR. IKEDA:** The first issue of the patient
2 with the known cancer can be an issue for the
3 current **BIRADS** codes in that the way that cancer is
4 being treated now is much different than it was
5 even five years ago. For example, a patient who
6 has a 5 cm breast cancer in the past would get a
7 mastectomy, whereas, now many of these patients are
8 getting neoadjuvant chemotherapy.

9 For those of you unfamiliar with this,
10 this is the patient gets chemotherapy before the
11 tumor is removed, and so the reason for imaging and
12 for doing the chemotherapy is to watch the tumor
13 shrink, so, for example, the patient may have a
14 mammogram with a suspicious tumor, gets a **BIRADS 5**,
15 highly suggestive of malignancy.

16 Six months later, after four rounds of
17 chemotherapy or three rounds of chemotherapy, what
18 the oncologist wants to know is has the tumor
19 shrunk.

20 They know there is a cancer there, for
21 example, and so we are in the unfortunate position
22 of saying yes, there is a tumor there, and then
23 they get another **BIRADS 5** suspicious for
24 malignancy, and everybody knows it is there.

25 I think that there was movement afoot of

1 perhaps adding another code, BIRAD 6, known cancer
2 present, to address this and to reflect the
3 changing of how breast cancer is being treated, and
4 so that these patients aren't being scared to death
5 with a letter saying, hey, there is a cancer, they
6 think they have a new cancer, and then they are
7 frightened, and that's horrible.

8 I think that that would be something
9 reasonable if that was approved by the BIRADS
10 Committee.

11 MS. HARVEY: Ms. Pura.

12 MS. PURA: Linda Pura.

13 Dr. Finder, I concur with you on the
14 Category Zero, not only is the client who is very
15 confused and very scared, but our primary care
16 clinicians also interpret this in very strange
17 ways, so I would like to ask for a clarification on
18 Category Zero on the BIRAD scale.

19 DR. PISANO: I guess I can provide it.
20 Category Zero is intended to be, at least when a
21 patient is in the process of being worked up. It
22 is not intended to be the final assessment
23 category.

24 So, we, at UNC, only use it when we do
25 screening mammography to say we read our screens in

1 patches and we interpret them. Basically, the
2 patients either get a zero or a 1 or a 2. That is
3 just the way we have decided to do it, and I am
4 sure this varies from some people use 4's and 5's
5 in the screening setting, too, but we actually
6 bring everybody back in for the complete workup,
7 make sure they didn't have a biopsy there causing
8 the spiculated mass, for example, talking to them
9 one on one.

10 So, I think in most settings, zero means
11 we still have to do more tests before we are sure
12 whether something needs a biopsy or not, but
13 perhaps it is being used differently than that in
14 some centers, I don't know.

15 MS. HARVEY: Dr. Kopans.

16 DR. KOPANS: I am on the BIRADS Committee
17 and there is discussion about Category Zero in
18 terms of use if someone is waiting for old films.
19 I think it is going to come out that that is an
20 inappropriate use of Category Zero. As Dr. Pisano
21 just said, the categories were set up to you are
22 evaluating the study now and what is your final
23 assessment now.

24 If you need additional evaluation, that is
25 a Category Zero. If you are waiting for old films,

1 you interpret the study as if you don't have the
2 old films, and Category Zero therefore is not
3 appropriate unless there is something that needs
4 additional evaluation.

5 So, the people who are saying they don't
6 know how to use it, they are not using it properly
7 if they are using Category Zero that way.

8 MS. HARVEY: Thank you.

9 Yes, Dr. Pisano.

10 DR. PISANO: I just want to make another
11 comment about it. In our center, it is sometimes
12 difficult because the two breasts have different
13 assessment categories, and we are supposed to
14 dictate one final assessment category, and we have
15 been cited actually on inspection, because we put
16 this is a 5 on the right breast and a 3 on the left
17 breast.

18 In fact, that is kind of a good
19 communication skill. When you were talking before
20 about burying information in the report, we would
21 like the final word on each breast to be in the
22 conclusion. You know, you don't want them to
23 forget about the 3 in the other breast, the one
24 that has to be followed in six months just because
25 you found a cancer in the other breast.

1 So, I would like to see some flexibility
2 about that built into the advice to clinicians, and
3 I am looking forward to the new BIRAD scale because
4 we do have all these other problems you have
5 mentioned.

6 DR. FINDER: The issue that you bring up
7 has been brought up before about the use of
8 assessment categories for each breast. That kind
9 of shifts the problem down one level because if you
10 still have two lesions in one breast, you still
11 have the same issue.

12 The question really I guess is, is should
13 these assessment categories be for each lesion
14 rather than overall, and if so, it would require a
15 change in the regulations obviously or at least our
16 implementation of them, but as I said, we did have
17 the situation where multiple lesions were
18 identified this way, and unfortunately, the
19 malignant one was buried in the middle of a whole
20 bunch of other benign processes.

21 It is one of those things where no matter
22 what you do, you create another problem somewhere
23 else.

24 MS. HARVEY: Dr. Kopans.

25 DR. KOPANS: The issue again I think of

1 multiple assessment categories, the report is still
2 there, and every physician is supposed to read the
3 entire report, not just the final assessment
4 categories. The final assessment category is
5 supposed to be a summary, and I think the BIRADS
6 Committee would come down on the fact that it is
7 the most important, which is what Dr. Finder
8 already said.

9 If you are just going to repeat the whole
10 report in the assessment categories, it becomes a
11 little redundant and silly, I think.

12 DR. FINDER: Dr. Kopans, what is your
13 feeling or do you know what the BIRADS group is
14 thinking about in terms of assessment categories
15 for each breast?

16 DR. KOPANS: To be honest, I hadn't
17 actually heard that as an issue. It may be, they
18 are reviewing a whole bunch of things at this
19 point. Again, BIRADS was designed to simplify the
20 report, and the issue of what BIRADS does versus
21 what the FDA requires, I suspect probably are two
22 different things.

23 I don't think that the committee is going
24 to change to an assessment for each breast, but I
25 don't think that has been decided.

1 DR. PISANO: When I made my comment, I was
2 really referring to FDA regulations because the
3 BIRADS Committee, I don't think anybody from ACR
4 would object if, in the interest of clarity, you
5 said in your conclusion, you know, there is a
6 cancer in the right breast, but there is also
7 something in the left breast that needs to be
8 followed at six months, it is probably benign.

9 That just fits the way we do mammography,
10 and I agree with Dan in reading the whole report,
11 but sometimes you do need to call out the most
12 important information. I am concerned because we
13 were cited because we did that at an FDA
14 inspection, so I feel like that is good medicine to
15 bring out the most salient points in the
16 conclusion, and yet if it conflicts with--we
17 actually had to change our practice, so we didn't
18 put it in our conclusion, which seems kind of silly
19 to me.

20 DR. FINDER: Let me just talk about that a
21 little bit. We do have guidance actually that
22 addresses the issue **of** the calling or labeling each
23 breast with its own assessment category. It is
24 allowed under the regulations, but what we also say
25 is if you are going to do that, then, you have to

1 have one overall assessment category.

2 But you certainly are free under the
3 regulations to do it that way, but if you are,
4 then, you have to have one overall assessment
5 category. That is the way the regulations are
6 pretty much written and interpreted.

7 One thing I do want to mention is one of
8 the reasons we came up to that conclusion didn't
9 have to do so much with the assessment categories
10 as the fact that at least in the beginning, there
11 were facilities that when they divided the reports
12 up into right and left breast, they were counting
13 those as two studies, and they were using those to
14 meet continuing and initial requirements by
15 dividing up the mammogram into two studies that
16 way.

17 So, in order to stop that, we said that it
18 is per patient, not by breast, and that is how we
19 ended up where we were with the assessment
20 category, so it all ties into that. There usually
21 is a method to how we come up with these things.

22 DR. KOPANS: Another way of working around
23 this if there are multiple final assessments that
24 are important, you can put just before the FDA
25 statement, "Please note there are multiple

1 important findings, the most significant is," and
2 when the--

3 DR. FINDER Right. There is a lot of
4 flexibility in terms of what the report can contain
5 and how you write it. We don't mandate the makeup
6 or the format of the report, but what we do say is
7 there has to be an overall assessment category.
8 That is the one thing that we pretty much do
9 require.

10 MS. HARVEY: Thank you.

11 Any more comments? Yes, Dr. Ikeda.

12 DR. IKEDA: I am a little concerned about
13 adding a second assessment for the second breast.
14 I am concerned about missing the most--1 thought
15 the intention of FDA was that the most suspicious
16 finding not be missed and be acted upon, and so if
17 you have, instead of 10,000 reports, you have
18 20,000 going out, I am concerned about that patient
19 having her cancer missed.

20 So, as far as the regulatory
21 recommendation, I know that you can put down the
22 multiple assessments, but I think the overall
23 assessment for the one patient is a good idea and
24 to keep it simple, so she gets treated for her
25 cancer.

1 MS. HARVEY: Dr. Young.

2 DR. YOUNG: Don Young. I would emphasize
3 that also. I still have referring physicians call
4 me and say what do you mean by "probably benign."
5 Adding another layer, assessment layer or two or
6 three is going to confuse the patients and the
7 referring physicians.

8 We cover these things in the body of the
9 report, as has been brought out earlier, and you
10 can phrase your report in such a way that it
11 mandates see above, paragraph 2, if you get into
12 two paragraphs. I try to avoid two paragraphs.

13 MS. HARVEY: Dr. Pisano.

14 DR. PISANO: Actually, it may be my
15 suggestion was being interpreted differently than
16 what I was really suggesting. I am not suggesting
17 that we increase the number of requirements in the
18 conclusion.

19 I am suggesting that we not be cited if we
20 do mention the opposite breast in the conclusion
21 besides the one with the most suspicious finding.
22 I mean that is what we were cited for, and I wish
23 that the guidelines to the inspectors would be
24 clearer, that it is allowed to use what you just
25 said, Charlie, a few minutes ago, about the report

1 was some flexibility.

2 I feel like we should have some purview
3 over good clinical practice in this area. There
4 are times when you know the referring physician,
5 you know how they read their reports. You know
6 that you need to emphasize both things, and I feel
7 Like that is a doctor's decision, we shouldn't be
8 told not to do it if it's good clinical practice.

9 So, that is the point I was making, not
10 that we should start doing it on every one, that is
11 the last thing I want is more paperwork and more
12 time spent by me. I want the ability to do it if I
13 have to.

14 MS. HARVEY: Any other comments? No?

15 Thank you.

16 I think we have come to a natural stopping
17 point for lunch. We will return at 1 o'clock.

18 Thank you.

19 [Whereupon, at 11:45 a.m., the proceedings
20 were recessed, to be resumed at 1:00 p.m.]

1 AFTERNOON PROCEEDINGS

2 [1:00 p.m.]

3 MS. HARVEY: Dr. Finder will speak first
4 on our topic of Full Field Digital Mammography.

5 DR. FINDER: I just wanted to expound a
6 little bit about some of the things that were said
7 earlier this morning about the way that full field
8 digital units are currently handled and the need to
9 have them hooked up to a film-screen unit.

10 Just to give you a little bit of
11 background and history on how we ended up where we
12 are, when the first full field digital unit was
13 approved by FDA for commercial use in early 2000,
14 there was no accreditation body that existed in
15 order to accredit those units.

16 Now, we deal under the Mammography Quality
17 Standards Act, and that Act requires that these
18 units be or that the facility be accredited and
19 certified. The only way we could handle this under
20 the situation was to tie a full field digital unit
21 to an otherwise already accredited and certified
22 film-screen unit.

23 That is the way that we have been handling
24 it in the interim until an accreditation body is
25 approved. It is not the optimal situation, but in

1 addition to keeping us compliant with the law, it
2 also gives us some assurance that the people that
3 are involved with the full field digital unit also
4 have some experience with film-screen and are
5 capable of becoming fully accredited with the
6 film-screen unit, so that does give us a sense of
7 security for these people to use the FFDM unit.

8 So, as has been stated in the morning,
9 yes, we do require that currently, because there is
10 no accreditation body out there, that if a facility
11 wants to have a full field digital unit, it in some
12 manner has to be tied to an accredited and
13 certified film-screen unit.

14 In order to make this as viable as
15 possible, we have expanded out our ability to tie
16 that unit to another facility, and has been stated
17 in the morning, it isn't necessary for the two
18 units to be actually physically in the same place.
19 We have allowed some leeway there.

20 The alternative, if we didn't do this, was
21 basically to say that since there is no
22 accreditation body and no other method to deal with
23 this, that you can't use it at all, and we didn't
24 find that to be acceptable, so we came up with this
25 method that kept us within the legal constraints,

1 also gives assurance that the people that were
2 using this were capable of otherwise accrediting or
3 capable of performing quality that would get them
4 accredited for their film-screen unit.

5 So, I just wanted to clarify that before
6 we go on any further.

7 MS. HARVEY: Thank you.

8 Our next presentation this afternoon is
9 Dr. Etta Pisano. She is going to talk to us about
10 the ACRIN Trial of Full Field Digital Mammography.

11 Dr. Pisano.

12 **ACRIN Trial of Full Field Digital Mammography**

13 DR. PISANO: Thank you.

14 [Slide.]

15 As I mentioned earlier, the National
16 Cancer Institute has funded a trial, which is a
17 screening trial for asymptomatic women, through the
18 American College of Radiology Imaging Network,
19 which some of you may or may not know is a new
20 cooperative group.

21 The trial is slated to cost about \$27.5
22 million. It is supposed to last three years total,
23 and it is underway as of last October.

24 [Slide.]

25 A screening trial, as I mentioned, is one

1 for asymptomatic women, women who do not have lumps
2 or discharge, women who would normally present to
3 the centers where the trial is open for screening
4 mammography.

5 [Slide.]

6 Women undergo both digital and film
7 mammography as part of the trial, and then the
8 images, the screen-film mammogram, and the digital
9 mammogram, all four views, of course, the same
10 /standard four views are taken for each exam are
11 read independently, so that one reader reads the
12 film exam and another reader reads the digital
13 exam.

14 The same reader does not read all the film
15 exams, and the same reader does not read all the
16 digital exams. The readers are split evenly
17 between the two conditions, so that if you are
18 reading on patient A, reader 1 will read the film
19 and reader 2 will read the digital, and then for
20 patient B, they read in the opposite conditions
21 across all the images acquired at their site, so
22 that it should be about evenly split across all the
23 readers at the site.

24 There are a variable number of readers at
25 the different sites. Some sites only have two

1 readers and some sites have as many as five to
2 seven readers. It depends on the number of people
3 that are qualified to read digital mammograms.

4 If one exam is positive, the patient
5 undergoes a workup for that exam. If both exams
6 are positive in the same area that the workup
7 occurs, and if they are positive in different
8 areas, workup occurs for all lesions found no
9 matter whether both exams are positive whether only
10 one exam is positive, and workup occurs as per
11 usual clinical protocols meaning if normally at
12 that site, additional views and ultrasound are
13 obtained after a positive mammogram, that is what
14 will happen after the positive film and/or digital
15 mammogram.

16 A negative mammogram is treated the same
17 way a negative mammogram is treated in any practice
18 with routine imaging and clinical follow-up,
19 meaning at a year for this study.

20 We do not have a lower bound for age, we
21 don't have an upper or a lower bound for age. We
22 are allowing the sites to determine which patients
23 they normally screen, so if a site starts screening
24 at 35, the woman is eligible for screening at that
25 site, then, she is eligible for the trial.

1 Some sites don't open their screening to
2 women until they are 40. Some women vary the first
3 age of screening with risk, so some women are
4 eligible to be screened starting at 25. If they
5 would normally be screened at that site, then, they
6 are eligible for the trial.

7 [Slide.]

8 Our outcome measures are going to
9 De--obviously, we don't have these yet--are going
10 to be ROC, assessment of the two technologies with
11 the primary outcome measure being area under the
12 ROC curve, which reflects both sensitivity and
13 specificity.

14 We are also going to measure positive and
15 negative predictive values. We are both going to
16 perform an assessment of digital mammography as a
17 modality and for each individual manufacturer,
18 because we can do that. We are going to have lots
19 of patients in each condition.

20 [Slide.]

21 I mentioned this already. It is
22 consecutive women. All women are approached, not
23 all participate, of course.

24 [Slide.]

25 The total numbers are somewhat staggering

1 . 49,500 women over a two-year period will be
2 enrolled.

3 I mentioned the trial will last for three
4 years. That is because we had to build in a year of
5 follow-up. At this point, there are 19 centers
6 open to accrual. Actually, this week we are
7 opening our 20th center. There are 29 centers that
8 are in the process of becoming open, in other
9 words, nine more still waiting to be opened.

10 We have 6 to 11 centers for each digital
11 mammography manufacturer that has equipment
12 available to be tested at this point. Trex is a
13 subdivision of Lorad, so I have Trex there, but you
14 can substitute Lorad for that.

15 [Slide.]

16 These are the names of the sites. These
17 are for the Fischer equipment.

18 There are a few minor changes on my slides
19 compared to what is in the handout. That is
20 because I sent it in a couple weeks ago and then I
21 found some errors. So, what is up on these slides
22 is correct, so if you notice changes, that is why
23 they are changed, is because I corrected my slides
24 after I sent it in.

25 So, these are the Fischer sites, and you

1 can see that we have a variety of types of sites.
2 We have academic practices. This is a private
3 practice here in D.C., Washington Radiology
4 Associates, as this is LaGrange Hospital in
5 Chicago.

6 [Slide.]

7 These are the Fuji sites. Mainly, these
8 are academic sites, these are all academic sites.

9 [Slide.]

10 The GE sites. We have more GE sites than
11 any other machine type, primarily because GE was
12 the first machine type that was FDA approved, so we
13 do have more machines in that category than in any
14 other category.

15 Originally, when we first opened the
16 trial, we envisioned balancing by machine type, but
17 we quickly realized that we needed more patients
18 than we thought we were going to need--well, the
19 same number of patients, but we couldn't get as
20 many patients per site as we were hoping to get, as
21 quickly as possible, so we added sites, and so we
22 ended up with this unbalanced per-machine type.

23 [Slide.]

24 These are the Lorad sites. Here is the
25 private group, Monmouth Hospital in New Jersey. I

1 think there were several in the GE sites that are
2 private groups, as well, so we do have a range of
3 types of settings.

4 [Slide.]

5 There will be 1,800-plus women enrolled at
6 each center. It is going to vary, of course, from
7 center to center, because our goal is to accrue for
8 two years, and some of the sites don't even come
9 open until after a year. We started out with the
10 idea that we would have 19 or 20 sites and that
11 there would be about 4 or 5 per machine type.

12 We quickly realized that the sites could
13 not enroll at the rate we were hoping, so we then
14 added another 10 sites, so that we are in the
15 process of adding those extra sites right now. So,
16 the numbers in terms of per-machine or per-site is
17 a little bit flexible.

18 Some sites, the ones that came up early,
19 will have higher numbers, some sites, the ones that
20 came up later, will have lower numbers per site, so
21 we are going to hope to accrue the 49,500 women in
22 a two-year period.

23 When we first opened, we thought we could
24 do it in 18 months, so we have had two adjustments
25 made just from the realities of accruing this many

1 patients per day. It was supposed to be 6 to 8
2 women per day getting two kinds of mammograms. You
3 can do the math and you can figure out how hard
4 that would be for sites.

5 They are doing it, they are doing quite
6 well, but it is a lot more challenging than we
7 originally thought. The interpretations are the
8 least of it, getting consent, filling in forms, all
9 the things that go with running a clinical trial,
10 it is very, very labor intensive, so we have
11 adjusted very rapidly to this information that
12 sites are not able to accrue as fast as we had
13 hoped they would.

14 So, this is the current plan, which is two
15 years of accrual. We started in October of 2001.
16 We are hoping to stop accrual in October of 2003,
17 more than a year from now. After that, we will
18 have a year of follow-up, which you must have a
19 year of follow-up for negative mammograms, at least
20 a year, to declare the patient cancer free.

21 In fact, probably that could be debated.
22 You might need as much as three or four years to
23 really know a patient didn't have cancer when she
24 had her mammogram, but for purposes of this study,
25 we are defining a woman's mammogram as a true

1 negative after one year **of** follow-up if she does
2 not have a diagnosis of cancer. Actually, the
3 exact range for follow-up is 10 to 15 months.

4 **So**, if a woman presents within 15 months
5 of that mammogram, the entry mammogram with the
6 cancer, we will consider the original mammogram a
7 false negative. I should say--I didn't make that
8 quite clear.

9 Anytime up to 15 months, the 10-month
10 period is when we must have, we are mandating a
11 follow-up mammogram of some sort. The earliest
12 after the original mammogram that can count as
13 being appropriate is at 10 months.

14 [Slide.]

15 Patients are excluded if they have a lump
16 or they have a bloody or clear nipple discharge.
17 If they have implants, they are excluded.

18 Implants require extra views of the
19 breast, and we didn't think it was appropriate to
20 include them because they would require four views
21 per breast times 2, so a lot of images, and we
22 thought it was too much radiation and we wouldn't
23 have enough numbers in that category to really get
24 statistical validity or statistical power, so we
25 excluded them rather than including them.

1 Anyone who is pregnant or thinks she may
2 be pregnant or if a woman can't undergo follow-up
3 mammography. We are not requiring that they come
4 back to the same institutions for their follow-up
5 mammograms because we wanted to open the trial to
6 as many people as we could, but they at least have
7 to provide the follow-up mammograms for review by
8 study radiologists.

9 [Slide.]

10 As I mentioned, we are doing two standard
11 views of each breast, and there is some tiling
12 needed sometimes, women sometimes have larger
13 breasts and the detector size for films and for
14 digital, so if a woman **is** too large for the
15 detector, for just one view in each projection, she
16 might have to have inners and outers, uppers and
17 lowers, just as we do with film mammography in
18 standard practice right now, and the same
19 technologist does both exams, and so she **is**
20 supposed to do both exams the same way.

21 If she has done inners and outers on the
22 film, she will do inners and outers on the digital.
23 We are not doing any extra diagnostic views during
24 the screening part of the trial. You can do
25 diagnostic workup with the digital system if it **is**

1 FDA approved, but some of the systems are not, at
2 Least one of the systems now, just the Fuji system,
3 is not yet FDA approved, so they cannot do
4 diagnostic workup using a non-FDA-approved system.

5 In addition, there are no extra views done
6 during the screening study. That is just not what
7 a screening study is. So, we are studying just the
8 screening exam in this study.

9 [Slide.]

10 I mentioned that the technologist is the
11 same. She has to be eligible to take mammograms
12 under MQSA. She is supposed to be using the same
13 degree of compression and the same angle with both
14 systems. That is definitely the case for the Fuji
15 systems since it is an image plate system where the
16 film is just replaced with the plate.

17 It is more challenging when you have to
18 move the patient between rooms, but they are
19 supposed to try to replicate the exams as much as
20 possible.

21 In addition, we are randomizing the order
22 of acquisition. We were worried about the
23 technologist being able to kind of tweak her
24 technique a little, if she saw the film mammogram,
25 she always did the film first and then did the

1 digital, she would then know that it was a
2 dense-breasted woman or something about the
3 patient, the way she compressed or something, and
4 make the other exam better.

5 So, that is why we are randomizing the
6 order of acquisition. That is assigned centrally.
7 When you register the patient for the study, you
8 are assigned a randomization, so you either perform
9 digital first or film first for all 49,500 women in
10 the study, that will happen.

11 We are trying to standardize the dose
12 between the two systems and if the AEC is
13 available, try to use it in the same manner for
14 both systems.

15 [Slide.1

16 As I mentioned, there are two radiologists
17 per patient, one to interpret each exam, one for
18 digital, one for screen-film. They are not
19 supposed to talk to each other. They are not
20 supposed to be aware of each other's
21 interpretation.

22 We have been careful at the sites to take
23 any little hints they might get about what the
24 other person thought. Every place has their own
25 way of making sure the patients are called and so

1 we have to inform them if they have a positive
2 mammogram. We have to pay a lot of attention to
3 that.

4 We go there to make sure that the second
5 radiologist can't figure out what the first
6 thought. We have **no** fellows or residents in the
7 room during the interpretation of these exams.

8 They are certainly free to be taught on
9 the images after the interpretations are completed,
10 but not until then, not until the radiologist has
11 entered his or her final interpretation, because we
12 were afraid of increasing the sensitivity of the
13 study if even a second person was reading, we don't
14 want that to happen across the study, **so** it is just
15 reader for the final reading for each set of
16 images.

17 [Slide.]

18 **As** I mentioned, we are splitting the
19 radiologists. I am a reader for this study, so I am
20 reading equally in film and digital, as **is** every
21 other reader. We started out with a requirement
22 that there would only be five readers per site, and
23 we soon found, because of people retiring and
24 quitting, and doing all the other things, that we
25 couldn't stick with this requirement, so this has

1 been dropped, there is no more than five readers
2 allowed at each site.

3 We have an executive committee that meets
4 weekly by conference call, and it consists of
5 myself, Ed Hendrick, who is the co-PI of the study,
6 and four radiologists, who are one for each machine
7 type, who has experience with each machine type,
8 plus the ACR personnel, plus Martin Yaffe, who runs
9 our QC program for this.

10 We meet weekly and we discuss issues such
11 as this, and five readers, it soon became apparent
12 that some of the sites started with five readers
13 and then lost people, and we didn't lost penalize
14 them, so we now require that all readers read
15 equally in each condition, and we try to have every
16 reader read more than 50 mammograms, which even
17 that is difficult to definitely require because of
18 the fact that we have had people start reading and
19 say I can't stand doing this, I am not doing it
20 anymore, and so you can't really penalize the site,
21 you can't throw those patients out because a reader
22 only wanted to read 20 cases, so we are keeping
23 those readings in the study.

24 [Slide.]

25 I mentioned already that we have no

1 trainees, just MQSA-qualified or would be, some are
2 Canadians, so would be qualified if they were
3 living in this country, or practicing in this
4 country, physicians.

5 We enter all data on-line, into a web
6 site, where the data forms are kept, so it's
7 on-line data entry for a lot of the data of the
a trial.

9 There also are worksheets that
10 radiologists can fill out because you can imagine.
11 I am a busy person, I don't want to sit there at
12 the computer all day entering data, so we have
13 forms that a person can fill out, instead of going
14 on line and entering directly themselves, and then
15 it can be entered later by someone.

16 You can enter on line, but you have some
17 flexibility about that. As I mentioned, if either
18 exam is abnormal, the workup should take place
19 according to the standard clinical protocols, and
20 even if only one exam is abnormal, even if you
21 think the other exam kind of clears the first exam,
22 you are supposed to work up the lesion, because,
23 you know, you might be interpreting the digital
24 mammogram differently or the film mammogram
25 differently given the first study. So, it is best

1 do just go ahead as if it is a regular clinical
2 workup on that patient, not refer to the other
3 exam.

4 [Slide.]

5 We use usual equipment and practices at
6 the different sites. At most, especially when we
7 first opened the trial, most of the cases were
8 worked up with screen-film mammography, but as I
9 mentioned, as they become FDA approved, we have
10 allowed people to be worked up with digital
11 mammography. Often senographe is used. Some sites
12 are using **MRI** and other imaging tests.

13 We are keeping track of all the downstream
14 costs of the positive exams, and of course, biopsy
15 is one of the most important outcome measures of
16 the trial. That is how we find out who has cancer
17 or not for the positive mammograms, the BIRADS 4
18 and 5 lesions.

19 [Slide.]

20 I already mentioned this. You can consult
21 widely with other experts if that is your normal
22 clinical practice for the workup. We don't control
23 the workup at the sites, so that if you want to
24 show it to three or four other radiologists before
25 you make a decision to biopsy, if that is your

1 normal clinical practice, that is not controlled in
2 the protocol. We want to know the truth about
3 these patients, so we are allowing people to do
4 whatever they normally do, and that might include
5 consultation with many others.

6 [Slide.]

7 We use the standard BIRAD scale, but that
8 is not the scale we are using for the primary
9 outcome measure in the trial. We are collecting
10 that for every patient for both digital and film.

11 We are also collecting the probability of
12 malignancy on a 7-point scale--I think I have it up
13 in the next few slides--and a call-back scale,
14 which is the probability that you think that the
15 patient needs to be called back with, how worried
16 are you basically.

17 [Slide.]

18 Here is the probability of malignancy
19 scale. It is just words, as you can see. We also
20 ask for the actual percent probability of
21 malignancy as a separate item, which I don't know
22 what good that is going to do us for sure, but we
23 definitely have collected that. There was a lot of
24 discussion of whether we just use the 7-point scale
25 or the 100-point scale. We are collecting both.

1 This is the scale that you must choose on
2 every single patient, you must give one of these 7
3 points. You give it for individual findings, and
4 then you do it for the overall assessment, similar
5 to what **FDA** requires, **so** you are supposed to
6 classify each individual finding and then classify
7 the whole mammogram.

8 So, this is the scale for that, definitely
9 not malignant, all the way to definitely malignant.
10 You can see there are gradations in between.

11 [Slide.1]

12 The call-back scale is a similar idea. We
13 are trying to get an idea of the level of
14 uncertainty that radiologists have in deciding
15 whether the patient should come back or not.

16 So, you might call something **BIRADS 1--I**
17 am just making this up, I am not thinking of a
18 particular case--you might decide to call something
19 **BIRADS 1** or maybe 2, but you think to yourself,
20 well, maybe there is some evidence the patient
21 should be called back for diagnostic workup, but I
22 am not going to call them back, I think it is below
23 my threshold, **so** you might give that a 2.

24 In other words, you are noting there is
25 something there, but something that is below your

1 threshold. The only things you have to give more
2 information on is the things you actually do call
3 back.

4 **So**, you can see all the way down from no
5 evidence to overwhelming evidence the patient
6 should be called back.

7 [Slide.]

8 We have, of course, follow-up, because
9 that will help us determine truth about the vast
10 majority of patients who have negative mammograms.
11 Patients are supposed to keep in touch with us.

12 We have a system where we are sending out
13 newsletters and keeping in touch with the patients.
14 The local sites have the contact information for
15 the patients, and they can contact the patients by
16 phone and mail.

17 Obviously, we would like them to all come
18 in for follow-up mammography. If they don't come
19 in, we have a way of calling them and finding out
20 whether they have been diagnosed with breast cancer
21 or not.

22 In addition, we plan, for the patients who
23 are lost to follow-up, make sure we check their
24 medical record at the hospital where they are
25 imaged and search tumor registries, and things like

1 that. I am hoping we don't have huge numbers of
2 women lost to follow-up because it is included in
3 the consent form that we expect them to come back
4 in a year and we are doing our best to keep up with
5 them, but some women will be lost to follow-up, of
6 course.

7 We are going to code follow-up information
8 on the mammograms. We need to know whether there
9 are new findings on the follow-up mammogram.
10 Basically, we are going to collect the BIRAD status
11 on the follow-up mammograms primarily because that
12 will help us determine the truth about that first
13 year's mammogram.

14 Obviously, if they have had any biopsies
15 in the meantime, we are going to collect
16 information on that, as well. We have central
17 over-read of all pathology.

18 It says 9 to 15. We have had a huge
19 debate about this. What I said earlier was 10 to
20 15 months, and I believe, I mean I wish I could
21 remember really straightforwardly right now, but I
22 think we actually changed it to 11 to 15 recently,
23 so I would have to check on that, but the reason is
24 because you want to be--obviously, if a patient has
25 breast cancer anytime up to 15 months, we are going

1 to call the first one a false negative.

2 The question is when do you allow yourself
3 to call it a true negative, how soon follow-up can
4 you have to call it a true negative, so there has
5 been a lot of discussion about that, and my
6 recollection now is that it is 11 to 15 months, so
7 this is slide is not correct.

8 [Slide.]

9 I mentioned this earlier, that there is
10 the team of physicists headed by Martin Yaffe at
11 the University of Toronto, and then helped by Ed
12 Hendrick who is the co-PI on the study. He is at
13 Northwestern University. They are overseeing
14 quality control at all these centers.

15 They are doing the MQSA requirements for
16 the screen-film units, and they are also sending
17 all the digital data and the screen-film data up to
18 Toronto where it is looked at centrally, as well.

19 In addition, we had a very comprehensive
20 acceptance testing protocol. Some of these
21 machines are not FDA approved yet. So, we are
22 making sure that they are functioning at a minimum
23 standard, what we have determined in advance prior
24 to the entry of patients into the study.

25 We have had no real glaring problems with

1 quality, no reasons to shut sites down or anything
2 like that during the--let's see, 10 months we have
3 been open at this point.

4 [Slide.]

5 We are also doing a cost effectiveness
6 analysis, which is, as I mentioned, we are keeping
7 track of all the downstream tests, and if someone
8 has both a positive digital and a positive film,
9 then, you can't really pull out which test caused
10 which, you know, which downstream cost, but you
11 will know that both would have caused those
12 downstream costs.

13 One of the hypotheses is that digital
14 actually has fewer false positives. That has been
15 shown in the other large screening trial that has
16 been performed by John Lewin and Ed Hendrick and
17 Carl Dorsey, which has been published already.
18 They did find a statistically significant lower
19 call-back rate and lower false positive rate, lower
20 false positive and lower biopsy rate.

21 So, that has been shown before with the GE
22 system in their big study, so we are hypothesizing
23 that will be shown again in our study, so we are
24 trying to figure out what that means in terms of
25 medical costs.

1 We are asking the radiologists to record
2 what additional tests are done on these patients,
3 and Dr. Anna Tosteson, who is a health care
4 economist at Dartmouth Medical School, will be
5 doing modeling to look at the cost effectiveness
6 issue.

7 [Slide.]

8 In addition, we have a patient telephone
9 survey that will be done on a subset of patients in
10 the trial. That was developed by Dr. Danny Fryback
11 of the University of Wisconsin, which we expect
12 fewer false positives, so we are trying to find out
13 how important that is to patients by interviewing
14 patients who had false positive mammograms versus
15 the control group.

16 Those are being done centrally, but
17 through telephone surveys, so it is a very short,
18 few-item questionnaire, and it is being done out of
19 UNC.

20 [Slide.]

21 All pathology reports will be reviewed by
22 one of two breast pathology experts. In addition,
23 the specimens of any breast tissue that is obtained
24 on patients during the course of the follow-up
25 period will be reviewed by the breast pathologist,

1 these same two breast pathologists, one of the two
2 of them.

3 In addition, if there is a disagreement
4 between a local pathologist and a central
5 pathologist, then, the other central pathologists
6 will be called in to give a tiebreaker vote, and
7 hopefully, there won't be a three-way disagreement,
8 but we may even have one of those, so we will have
9 to find a fourth person to kind of help us.

10 I don't have any data about how often this
11 is happening. I did just see the data from R.5 on
12 this, which was a multicenter clinical trial of
13 stereotactic and ultrasound guided core biopsy for
14 nonpalpable lesions, and the rate of disagreement
15 in that study was only 4 percent, which is very
16 good actually for a kappa number. It is 96
17 percent, 0.96 kappa is extremely high for any
18 technology.

19 So, I am hoping we have numbers like that
20 for this study.

21 [Slide.]

22 What I have described just now was what we
23 are doing to achieve our primary aims and I also
24 described some of the secondary aims because I
25 talked about quality of life and cost

1 effectiveness, but what I just described are the
2 main aims of the study or how we are achieving the
3 main aims of the study.

4 We are also planning additional studies
5 during year 3, after all the patients have been
6 acquired, all the images have been acquired, we are
7 going to run reader studies to assess other aspects
8 of digital mammographic performance, diagnostic
9 performance.

10 For example, a big issue is softcopy
11 display versus printed film display, does the
12 technology perform equivalently in both conditions.
13 Just as an aside, I didn't say this, but we have
14 assigned reader methods for each system. For
15 example, **GE**, all readers are reading in softcopy.
16 For Fuji, all readers are reading in hardcopy.

17 For Fischer, all readers are reading in
18 both conditions, both soft and hard copy, and for
19 Lorad, right now they are reading in hardcopy, but
20 they may be switching to softcopy. The point is
21 that we have standardized it across sites, so we
22 really can't answer this question, softcopy versus
23 printed film, within the study.

24 Really, it wouldn't be appropriate because
25 each system has its own softcopy system to really

1 make a statement across digital mammography for
2 soft versus hard copy, so what we are going to do
3 is run reader studies in the third year where we
4 compare digital softcopy to digital hardcopy for
5 each machine type, so that each new manufacturer
6 will give us their best version of their softcopy
7 system and will run reader studies comparing soft
8 to hardcopy for each manufacturer to determine the
9 diagnostic accuracy.

10 In addition, I am going to skip over the
11 second bullet for a second because it is kind of an
12 arcane statistical thing that I think the
13 statisticians will be happy we did them, it will
14 take me a few minutes, so we are going to look at
15 breast density and its effect on diagnostic
16 accuracy and compare digital film for that, because
17 the hypothesis is that obviously, people believe
18 digital may be better than film in dense-breasted
19 women, and so we are going to have a lot of data on
20 that by the end of this trial.

21 You know, this trial is costing \$28
22 million and doesn't even include all the systems
23 that exist in the world for digital mammography.

24 I am personally aware of two other systems
25 that didn't make it in time for this trial, there

1 may be others out there, as well, and we can't keep
2 running \$28 million studies every time we have a
3 new system, so the statisticians and those of us
4 who do clinical trials are very interested, isn't
5 there some other way we could do this without
6 having to run a full-fledged clinical trial, so we
7 are actually going to look at the use of a reader
8 study in predicting, and I know the FDA
9 statisticians at least over in the Device Approval
10 Branch are going to be interested in the result of
11 this study, is there any way to predict the results
12 of the full-fledged trial with carefully controlled
13 reader studies, can we estimate the diagnostic
14 accuracy.

15 We are going to do this study with that
16 percent prevalence in the reader sets to see if any
17 particular mix, case mix is most predictive of the
18 outcome.

19 I talked about this already as the
20 secondary aim. Each unit may have different
21 performance versus film-screen mammography. It is
22 possible that one unit really performs extremely
23 well and better than film. It is possible that
24 another unit performs less well than film, so we
25 really need to divide them up.

1 We have the whole technology kind of
2 lumped together in the overall aim, but we will
3 divide them up and look at them that way, as well.

4 Obviously, we have much less power for
5 this aim than we do for the overall aim of
6 comparing digital to film, but we do what we can
7 and obviously, we will have a lot of power for the
8 GE because they have a lot of systems out there
9 being tested in the trial.

10 We will have less power for the other
11 manufacturers because we only have six machines.
12 In addition, all these other characteristics will
13 be tested, digital versus film. Obviously, we have
14 less power against any of these than we do against
15 the main objectives - age, lesion type, pathologic
16 diagnosis, et cetera.

17 [Slide.]

18 We also have a lot of technical aims in
19 this trial. We have a big quality control program
20 going on, collecting a huge amount of data on a
21 daily, weekly, monthly basis. We are hopefully
22 going to have a pretty good handle at the end of
23 the trial on the effect of spatial and contrast
24 resolution on diagnostic accuracy, if there is such
25 an effect.

1 We have a range of image detectors in the
2 trial on the Lorad system that was available until
3 recently, which is getting discontinued, which is
4 the one that is FDA approved at this point, has a
5 41-micron pixel size, and the GE system has
6 100-micron pixel size.

7 In addition, we have a range of contrast
8 resolutions, 10 to 14 bits, and so we will have
9 some idea, we hope, about the importance of those
10 factors. We are going to have a good idea of
11 whether image quality varies tremendously across
12 sites and we hopefully will know about dose, as
13 well, and we are going to know about the range over
14 time, whether things change a lot, drift a lot, so
15 far there haven't been major surprises, but we will
16 have lots and lots of information about that.

17 [Slide.]

18 I just wanted to show you a few pictures.
19 It may be too bright in here to really appreciate
20 this. This is an image from the University of
21 Pennsylvania, and there is really two lesions here.
22 There is a big, obvious spiculated mass, and then
23 right next to it is a little smaller, indistinct,
24 irregular mass, which both were cancers. I assume
25 one was invasive ductal and the other was invasive

1 lobular, but I am not sure about that.

2 [Slide.]

3 Here is another example of an infiltrating
4 ductal carcinoma with DCIS, which was on the
5 Fischer unit. The first image I showed you was
6 from a GE system. This one is at the University of
7 Toronto.

8 So, I am happy to answer any questions.
9 We have a lot of times still, I only took 40
10 minutes. Does anybody have any questions about the
11 trial?

12 MS. HARVEY: Dr. Harrison.

13 DR. HARRISON: You mentioned in getting
14 pathology read that you were hoping that there was
15 not a necessity to break a three-way tie, you
16 either have malignancy or you don't. How can there
17 be a three-way tie?

18 DR. PISANO: Well, we have a 5-point scale
19 from pathology. There is malignancy, there are
20 obviously malignant, invasive ductal cancers, there
21 are obviously benign lesions like fibroadenomas and
22 things like that, but there are kind of gray
23 lesions like--

24 DR. HARRISON: It was rhetorical.

25 DR. PISANO: Oh, I know you know the

1 answer. You want me to clarify.

2 DR. HARRISON: Right.

3 DR. PISANO: LCIS and the lobular
4 neoplasias, lobular carcinoma in situ, the other
5 lobular neoplasia lesions. There can be quite a
6 bit of disagreement between pathologists around
7 those kind of high-risk lesions.

8 That is where we found disagreement in the
9 R.5 data is right at that point. We did very well
10 overall, but that group had a higher rate of
11 disagreement, and then DCIS, of course, sometimes
12 there is disagreement in classifying a lesion as
13 ductal carcinoma in situ, so we do have a range of
14 possibilities.

15 Hopefully, the pathologists will agree
16 most of the time, but we don't want it to be too
17 high a rate. I don't expect a very high rate.
18 Frankly, the R.5 data was better than we expected.

19 It was earlier studies that indicated as
20 much as 7 to 10 percent disagreement rate between
21 pathologists with open biopsy. So, we were
22 pleasantly surprised to see it was smaller than
23 that for R.5, and presumably that suggests a
24 training effect over time. Maybe people are
25 learning, they are not so unfamiliar with these

1 border cases.

2 MS. HARVEY: Dr. Lee.

3 DR. LEE: I was wondering if you had a
4 sense of out of the women who are eligible for the
5 study, what percentage actually are participating.

6 DR. PISANO: I don't really know for sure.
7 I can tell you about my site. We actually have two
8 machines going in two different buildings, and we
9 have more women, we have lots of women who want to
10 participate. It is mainly the rate limiter is not
11 the number of women who want to participate, it is
12 more just physically, how many mammograms can you
13 do a day.

14 You know, you are using these machines for
15 clinical work, and you have to kind of fit in the
16 research into the clinical day, and there is only
17 so much you can do. We are taking all comers who
18 want to do it, but you can't keep working until
19 midnight.

20 So, that is really not the issue that
21 patients aren't willing to do it. We have lots of
22 patients willing to do it. That has not been our
23 problem at all. It is more just physically being
24 able to handle that much per day. It is very, very
25 labor intensive.

1 MS. HARVEY: Dr. Ramos.

2 DR. RAMOS-HERNANDEZ: Because of the
3 disparities among different ethnicities and the new
4 tendency for African-Americans and Latinos to be
5 diagnosed at younger ages, in the general
6 information that you are getting, some sense, or
7 are you collecting specifically age and ethnicity,
8 so when we get results, we have a sense, see if
9 this is more accurate for specific groups?

10 DR. PISANO: Yes, we are collecting age
11 and ethnicity, and, in fact, we have been
12 monitoring very carefully our African-American and
13 Hispanic and Asian enrollment in the trial.

14 We noticed in the first six months of the
15 trial that we had fewer than we would like both in
16 African-American and Asian and Hispanic women. We
17 had appropriate percentages of white women and
18 Asian women.

19 So, we actually have targeted
20 interventions directed toward the minority
21 populations that we have put in place at specific
22 sites. What we did was we looked at the
23 demographics at the sites that had more
24 African-American and Hispanic women, and we have
25 asked those sites to target those populations in

1 specific ways.

2 We have noticed already that we are
3 getting reports from the Data Safety and Monitoring
4 Board and the Statistical Center, we get monthly
5 reports, and the ethnicity report we got in April,
6 we have already seen a correction, so we have
7 gotten the numbers back up to where we want them to
8 be or I should say up to where we want them to be
9 already from where they were, which was not
10 acceptable or below what we thought it should be in
11 April just by getting a couple sites to make
12 outreach into the community.

13 Actually, Washington Radiology is one of
14 the sites that we targeted, and Denver, the
15 University of Colorado, both those sites.
16 Washington Radiology and Denver both had large
17 numbers of Hispanic patients, and so we improved
18 the enrollment for Hispanic patients by basically
19 having translation of consent and available person
20 at the site who can speak Spanish, things like
21 that, simple things like that.

22 In addition, the NCI has a communications
23 kind of guru, someone who could help clinical
24 trials recruit patients and target certain
25 populations, and they have been quite helpful in

1 coming up with strategies. So, we have dealt with
2 that issue. I don't know whether there will be a
3 difference, but we will look at it, the ethnicity
4 of the patients as one of the factors affecting the
5 outcome of the trial, we will look for it.

6 DR. RAMOS-HERNANDEZ: Since the beginning
7 of the trial, did you set up specific percentages
8 of special populations that you wanted to achieve?

9 DR. PISANO: What we did was we looked at
10 the U.S. population and we are trying to reproduce
11 the percent of the population studied that reflects
12 what Hispanic, African-American, Asian, white, are
13 in the population.

14 We probably are not going to succeed in
15 doing that exactly, but we are going to come as
16 close as possible to it as we can with these
17 interventions that we have created or are
18 undertaking.

19 MS. HARVEY: Dr. Harrison.

20 DR. HARRISON: Along the same lines,
21 historically, African-American participation in
22 clinical trials has been very low, down around 1
23 percent. What are the numbers that you are seeing
24 right now?

25 DR. PISANO: Well, we are seeing much

1 better than that, but I don't remember the exact
2 figure off the top of my head, but my memory is it
3 is closer to 10 or 15 percent African-American,
4 maybe even higher than that. I really don't
5 remember the exact numbers, but we are coming close
6 to the percent in the population at the different
7 sites.

8 For example, Alaska, Native American, we
9 don't have any sites that are really in places
10 where there are Native Americans, so we can't
11 possibly achieve the percent that really exists in
12 the population of that particular subset of the
13 population. We are doing what we can.

14 I will say at my site, we are definitely
15 getting a percent of women who exist in our
16 population. At UNC, it is about 30 percent
17 African-American, and we are getting about 30
18 percent African-Americans at our site, but I don't
19 remember the exact numbers at the rest of the sites
20 overall. I would have brought the figures, I mean I
21 can provide them if you are interested, but I don't
22 have them with me today.

23 DR. HARRISON: Are **you** allowing people
24 with previous cancer diagnoses to be screened?

25 DR. PISANO: The answer is if a woman has

1 had a mastectomy, and she would normally get
2 screening mammography for the opposite breast,
3 then, she is eligible to participate in the trial.
4 Some sites do not image women as screening
5 mammograms who have ever had a cancer diagnosis, so
6 those sites, those women are never screened--

7 **DR. HARRISON:** Right, they are always
8 defined as diagnostic at that point.

9 **DR. PISANO:** They are always diagnostic.
10 Now, women who have had lumpectomy and radiation or
11 without radiation are not eligible because those
12 women, we define them as needing diagnostic
13 mammograms as opposed to screening mammograms, but
14 women who have had mastectomy can participate if
15 that center performs those patients as screening
16 mammograms.

17 **DR. HARRISON:** Right, because presumably,
18 the contralateral breast does not have
19 architectural disturbances that we have created.

20 **DR. PISANO:** Exactly.

21 **MS. GILBERT:** I know that you did address
22 this earlier. What are some of the strategies that
23 you are using to recruit these women? 49,000 women
24 are a lot of women. Can you just give me some idea
25 of what you are doing?

1 DR. PISANO: Well, the centers that are,
2 first, the centers that are participating in this
3 trial are all high-volume centers. We don't have
4 anybody who does five mammograms a day or anything
5 like that, so we are not talking about centers that
6 have no population to recruit from.

7 The primary thing we do is publicize the
8 trial at the centers where there already are
9 screening mammograms happening in large numbers per
10 day. At my site, it is over 70 screening
11 mammograms per day. So recruiting 15 of those
12 women, you know, 10 to 15, some number like that
13 every day has been no problem.

14 On top of that, there has been local
15 publicity at the local sites. I mean it is kind of
16 a tradeoff. You don't want to distort the
17 population at the site away from the screening
18 population. You know, it is a little bit of a
19 mixed blessing getting other women in who don't
20 normally come to that site for screening.

21 Certainly, you want people to know about
22 the trial, but perhaps people will come to get
23 screened who wouldn't ordinarily or should not be
24 screened. So, we want to make sure that women who
25 will come to the center for screening, we want to

1 be able to make sure they come back in a year for
2 follow-up, so we publicized it locally.

3 Each center has brochures they can
4 distribute to local primary care physicians or to
5 women's groups locally. We send it out. At **UNC**,
6 for example, they sent it to local PTAs, we have
7 sent these brochures out, we have done all sorts of
8 things like that.

9 I am not sure how many patients for sure
10 come in because of that, but we do have some
11 publicity. There is a web site for the trial,
12 which is a very attractive, nice place to come
13 visit, and it gives very explicit instructions to
14 patients on how to get a mammogram appointment at
15 the site if they are interested in participating,
16 or to women, I should say, these are screening
17 women, they are not really patients.

18 If women want to come in to the centers
19 for screening, they can come in based on the
20 instructions at that site, but occasionally,
21 patients, you know, we have to be vigilant that
22 patients who aren't eligible for screening might
23 get into the trial. We don't want that to happen
24 with this trial, as it has happened in other
25 clinical trials.

1 We want patients to really be asymptomatic
2 patients or women--I am getting my terminology
3 nixed up--but we want women to come in who have no
4 problems, and if they are symptomatic, they
5 shouldn't be part of the trial.

6 We have done a lot of stuff, but, as I
7 said, you have to be careful that you don't almost
8 overpublicize it to the point where people who
9 ordinarily aren't getting screened are coming in,
10 maybe 20-year-olds. I did have a 20-year-old come
11 up to me after I gave a talk on it and asked me how
12 she could be part of it, and I had to tell her,
13 sorry, you are too young to be screened.

14 MS. GILBERT: Is there an age range that
15 you are looking at?

16 DR. PISANO: Well, as I said, the centers
17 screen a population of women, and there are some
18 women who are eligible for screening below the age
19 of 40, and so those women, if they come normally to
20 that center for screening mammography, for example,
21 if you are at high risk for breast cancer, your
22 mother had breast cancer at age 40, at UNC, we
23 start screening those women annually at age 30.

24 So, those women come to UNC for routine
25 appointments now, they show up on our schedule for

1 screening mammography now, they are recruited to
2 the trial, we don't exclude them.

3 Obviously, we don't want to have too many
4 women that are at low risk, and some women are
5 worried about their breasts and start screening on
6 their own at a young age, and we are kind of
7 leaving that up to the local sites to make the
8 decision would they normally screen these patients.

9 If they would normally screen these
10 patients, they are eligible for the trial. We
11 don't really have a lower age cutoff.

12 There is a long discussion about that. We
13 talked about cutting it off at **40**, but there are
14 really high-risk women who wanted to participate in
15 the trial, so we decided we would err on the side
16 of including them as opposed to cutting them off
17 because of their age.

18 MS. HARVEY: **Ms.** Rigsby.

19 MS. RIGSBY: Do you charge the ladies that
20 come in for the screening?

21 DR. **PISANO**: We do charge them for film
22 mammography. They get the digital mammogram for
23 free, so it is really their insurance, most of them
24 have insurance, some don't. The ones who don't,
25 they have to pay for their film mammogram out of

1 :heir pocket or whatever way they normally pay for
2 it. We don't have, believe it or not, \$27.5
3 million, enough to pay for the full mammogram, too.
4 It's a huge undertaking with this many thousands of
5 women.

6 MS. HARVEY: This is a phenomenal amount
7 of data that you are collecting. When will we
8 expect to see the first reports of your findings?

9 DR. PISANO: If we wait until all the
10 follow-up is in, that would be October--it will
11 probably be December, you know, given a few extra
12 months there, the 15 months as opposed to the 12
13 months, it will be December of 2003. That is until
14 all the data **is** in from follow-up.

15 Obviously, we will have some preliminary
16 idea before then, at least the statisticians will.
17 My guess is sometime in 2003, there will be
18 something, but I don't know exactly what month that
19 would be.

20 MS. HARVEY: Thank you. Any other
21 questions? Dr. Karellas.

22 DR. KARELLAS: I have two questions. If a
23 patient asks for her original films because she is
24 going somewhere, moving somewhere, how do you
25 handle that?

1 DR. PISANO: In the consent form for this
2 study, we ask their permission to keep the films
3 centrally, so the women relinquish their films to
4 the study. That is so that we can do these reader
5 studies during the third year of the trial.

6 If they need the films back for clinical
7 purposes, which is quite possible, they can be
8 requested, and we ask them to send them back after
9 they are finished with them. So, the patients
10 aren't keeping their own films right now, they are
11 all being stored.

12 The digital images, a copy of them is
13 being stored in ACR Imaging Network Headquarters in
14 Philadelphia, and the original film mammograms are
15 being stored in ACR Imaging Network Headquarters in
16 Philadelphia.

17 I had recently a patient who came in with
18 a problem about three months after her film
19 mammogram, and we got it by FedEx, her old films,
20 within 24 hours. That happened to me at UNC, so I
21 know it is working. It has worked for that one
22 case anyway.

23 That is an experience we have had in the
24 past, that we can get the cases pretty quickly back
25 if need be.

1 **DR. KARELLAS:** Have you thought of how you
2 and all the sites would handle if a percentage of
3 these patients want a copy of their digital
4 mammograms at some point?

5 The reason I am asking you that is that I
6 am finding it very difficult to deliver digital
7 mammograms to people who want them, and it is okay
8 when they want one or two or three a year, but it
9 is very difficult to envision if we have 100
10 patients in a week ask for their digital data, it
11 is very time-consuming.

12 **DR. PISANO:** I don't know if I have any
13 information from within the trial, but I will talk
14 from my own personal experience as someone who has
15 digital mammography in my practice. I have not
16 found this to be a big problem where patients are
17 asking for their images a lot.

18 **As** I mentioned, we have two digital units
19 doing clinical work plus we have another one
20 participating in the trial, so I have not had a
21 real problem with patients requesting their images.

22 What we have done when they have
23 requested, we have a printer and we just print out
24 another copy and hand it to them. **If** everybody
25 were asking for it, it would be exorbitant, but we

1 haven't had that many patients, just as most
2 patients don't want to keep their film mammograms,
3 we haven't had that many people request that, so it
4 hasn't been a problem in our practice.

5 **DR. KARELLAS:** The reason I am asking
6 about that, it is very easy if they request it at
7 the time of examination. It is always more
8 difficult if they come back a year later, because
9 the images are not just all neatly packed in one
10 place on patients, so there can be various CDs or
11 various locations, so that is something for the
12 sites to think about as to how this could be
13 handled in the future.

14 **DR. PISANO:** That is a good point. I
15 haven't had anybody ask me for the mammogram except
16 at the visit where we did the mammogram, but you
17 are right, if it is even a week or two later, and
18 it has already been archived, it is a little bit of
19 a challenge to get that case back and printed, but
20 it wouldn't be impossible.

21 Of course, you could always hand them the
22 one you have in the jacket, knowing you could print
23 another one in a few days or something while you
24 search for it.

25 We don't have a good pack solution at UNC,

1 I wish I did, but I don't.

2 MS. HARVEY: Thank you. Excellent talk.

3 We have a few minutes while we prepare for
4 Dr. Kopans' computer to get set up, which might be
5 a good opportunity for us to discuss any questions
6 that any of the board members might have up to this
7 point or any other issues that you would like to
8 talk about. There is lots to think about with the
9 digital. It is going to be the wave of the future.

10 Dr. Harrison,

11 DR. HARRISON: When, in fact, a suspected
12 malignancy is found in these clinical trials, the
13 clinical handling of that is done by the local
14 clinicians?

15 DR. PISANO: I should have mentioned that
16 in the talk probably. Each site handles the
17 identification of abnormal mammograms and the
18 biopsies and everything else as per their usual
19 clinical protocol.

20 For example, at my site, we wait until
21 both mammograms are interpreted, and we have a
22 nurse who contacts the patients and tells them
23 about the positive exams, so that person makes the
24 phone call.

25 Instead of just saying you had an abnormal

1 screening mammogram, you need to come back for
2 additional views, she says you had an abnormal
3 digital or you had an abnormal film or you had
4 both, an abnormal digital and film, and you need
5 additional views.

6 Then, the letters they get include both, I
7 mean everything has been adapted for the trial.
8 The primary care physician gets a dictation that
9 says, in our case, I am talking about UNC--each
10 site had to do what their IRBs would let them do or
11 wanted them to do--so, at UNC, first, they get a
12 report, the primary care physicians get a report
13 that says film mammogram report with a signature,
14 digital mammogram report with a report and a
15 signature, and somewhere in the report, put on by a
16 secretary at the top, is this patient participated
17 in digital, she received both a digital and film
18 mammogram, so that the primary care physician gets
19 both reports, knows what is going on.

20 When we get the patient back for workup,
21 the radiologist dictates into the final report,
22 this patient had both, was part of this study, had
23 an abnormal whatever, and we did the workup of
24 this, this way, we did the workup of that, that
25 way, and the final interpretation category.

1 So, we have adapted everything to this
2 trial.

3 DR. HARRISON: One corollary question. Do
4 you certify a letter to the patient?

5 DR. PISANO: No, we don't send our letters
6 certified mail right now, we just send them regular
7 mail.

8 DR. RAMOS-HERNANDEZ: Is there anything in
9 the study or what would you do with people that
10 actually couldn't afford to pay the screening
11 mammography, but they are diagnosed, they get
12 something, an abnormality, and they are going to
13 get help to pay?

14 DR. PISANO: I am sorry, I am not sure I
15 understand your question.

16 DR. RAMOS-HERNANDEZ: Is there any support
17 for payment when finding an abnormal mammogram?

18 DR. PISANO: So, if the abnormal mammogram
19 occurs, is there any way to pay for the downstream
20 costs?

21 DR. RAMOS-HERNANDEZ: Yes.

22 DR. PISANO: There is no money allocated
23 at present in the trial to pay for downstream test
24 costs. That is part of the consent process, that
25 the patient would be responsible for those

1 downstream test costs.

2 That is the way we have dealt with it, is
3 just inform the patient upfront that she may have
4 additional costs if she is not insured. We have
5 had no insurance company refuse to pay for the
6 downstream costs that I am aware of.

7 MS. HARVEY: Thank you.

8 Dr. Kopans will talk to us about
9 tomosynthesis.

10 DR. KOPANS: And a few other things. I
11 come from Boston. I have to admit I am a little
12 anxious to not be standing with my back to the
13 wall, which is the way we are taught, so if
14 something is coming from behind, I wish you would
15 let me know and have me duck.

16 **Potential New Applications of FFDM**

17 [Slide.]

18 DR. KOPANS: I suspect that the committee
19 is well versed in digital mammography, but before I
20 get into tomosynthesis, which is really the main
21 thrust of my comments this afternoon, I just wanted
22 to briefly kind of review just so that everybody
23 understands digital mammography and why there are
24 multiple advantages to digital that are going to be
25 coming along.

1 I am going to actually speak about two
2 other aspects of digital other than tomosynthesis,
3 but I will do that briefly.

4 [Slide.]

5 Basically, a digital mammogram, the way I
6 think of it is a spreadsheet where you have got
7 rows and columns, and each row can be labeled with
8 a number and each column can be labeled with a
9 number, and then the x-rays that are collected at
10 each cell, if you will, or pixel, can be labeled
11 with a number.

12 **So**, for example, 60 photons--I am just
13 making these up--but 60 x-ray photons come through
14 and are collected in this cell, then, we know that
15 this is cell 5-5, and there are 60 photons, so we
16 can define the location and the number of x-rays at
17 that point in space by numbers, and hence, the term
18 digital, so that the whole image can be described
19 as rows, columns, and numbers of x-ray photons.

20 Then, we can manipulate that image because
21 we can assign different levels of gray or color if
22 we really want to, to help whoever is looking at
23 the image appreciate things that may not be obvious
24 with one sort of presentation.

25 **So**, a digital mammogram is just an image

1 made up of numbers, and, of course, that allows the
2 computer also to be brought to bear.

3 [Slide.]

4 I suspect the committee knows the basic
5 advantages of digital mammography - higher contrast
6 resolution, greater dynamic range than the
7 film-screen systems, because you are not exposing
8 the image to meet the parameters of the detector,
9 for example, the film-screen, you have to have
10 specific exposure values, otherwise, when you
11 process the image, it won't be a satisfactory
12 image.

13 With digital, you are actually uncoupling
14 the detector from the display, and you can adjust
15 the image afterward in any one of an infinite
16 number of display characteristics, but that way you
17 can image the breast, so that you get the imaging
18 characteristics, and you don't have to worry about
19 the display.

20 You can manipulate the image. We use
21 digital for real-time procedure guidance, I think
22 you probably know that, with stereotactic devices.
23 The areas where I think digital is really going to
24 have an impact over and above conventional
25 film-screen mammography are in the areas that I

1 have listed below.

2 I am not going to talk about
3 telemammography, but I heard you discussing issues
4 of some underserved women, and certainly being able
5 to transmit images from areas where there may be
6 remote access, digital mammography will permit
7 that.

8 We have actually sent images between New
9 York and Boston, the short way, 22,000 miles out to
10 a satellite and 22,000 miles back again. We did
11 that over 70,000 times without a single loss of
12 information. **So**, that is doable. You could be in
13 some remote area in, say, the western part **of** the
14 country and transmit images anywhere in almost
15 real-time.

16 [Slide.]

17 We use digital now, of course, for
18 procedure guidance. I am not going to spend any
19 time on this.

20 [Slide.]

21 There are multiple ways **of** doing digital
22 imaging. This is the image of a prototype
23 slot-scanning device that we actually had back in
24 the **1980s**.

25 [Slide.]

1 It was way before its time, and
2 unfortunately, the company didn't have the staying
3 power, but the Fischer system works in a similar
4 way with x-rays coming through a pre-breast slot
5 and then a post-breast collimator, and then
6 detected as a detector.

7 This is the system we had in the 1980s,
8 but it is similar to the Fischer where the detector
9 moves, it is a linear detector and it moves across
10 as the exposure is made. This has the advantage of
11 being very good at scatter rejection.

12 [Slide.]

13 This is just for historical purposes. I
14 think probably the first very high-resolution
15 digital study, again done in the 1980s with the
16 American Science and Engineering system, this is 9
17 line pairs/millimeter of a high-grade ductal
18 carcinoma in situ.

19 [Slide.]

20 Just one of the quick things you can do
21 with digital is if you don't like white dots on a
22 black background, you can just push a button and it
23 will be black dots on a white background.

24 Although this is more than a parlor trick,
25 sometimes just changing the image presentation can

1 make things more visible to the human eye than
2 other manipulations, so that sometimes just
3 breaking up our pattern recognition allows us to
4 see things that maybe we wouldn't have appreciated
5 in the conventional way.

6 With digital, this is just a push of a
7 button.

8 [Slide.]

9 There are other technologies. This is the
10 Fuji approach, which is a stored phosphor system
11 where a plate is stimulated by the radiation to a
12 higher energy level, and then that is read with a
13 laser. I am not going to go into the details of
14 the different technologies.

15 [Slide.]

16 This is just a mastectomy study we did a
17 number of years ago with the Fuji system.

18 [Slide.]

19 There are charge coupled devices, which
20 basically convert the x-ray photons into light
21 photons, and then the light is channeled down to a
22 charge coupled device, which converts the light
23 into an electrical signal, and that then goes to
24 the computer.

25 [Slide.]

1 This is actually the system that the
2 Fischer unit uses in somewhat of a linear array.
3 The initial Trex, Lorad, Bennett, I don't know how
4 many other companies, had this system, and then as
5 I think everyone knows now, Lorad has converted to
6 a selenium system, which I will mention again in a
7 second.

8 [Slide.]

9 These generally have to be put together in
10 some form of mosaic, because the charge coupled
11 devices aren't big enough to cover the entire
12 breast.

13 [Slide.]

14 This was the old Lorad system with 12.
15 Each one of these is a CCD camera with fiberoptics
16 in the screen that converts the x-ray photons.

17 [Slide.]

18 This is just from Lorad, a slide from
19 Lorad using selenium to convert the x-ray photon
20 directly to electrical signal without going through
21 a light conversion approach.

22 [Slide.]

23 Again from Lorad.

24 [Slide.]

25 This is from General Electric, which is

1 their system converts the x-ray photon to light and
2 then, in an electronic array behind the Light
3 conversion level, they convert the light into
4 electrical signal, and this is actually the reverse
5 of what we do with most of our computer displays
6 where there is literally a wire to every point in
7 the area.

8 The difference between this and the
9 selenium detector is that the x-ray photon is
10 converted directly to electrical signal in the
11 selenium detector, and in this, there **is** a light
12 conversion factor first.

13 [Slide.]

14 Again, you can imagine somebody having to
15 stretch these little, tiny wires to each one of
16 these points, so the manufacturing of these systems
17 is tricky, but I gather the companies are doing
18 pretty well with it.

19 [Slide.]

20 **You** have probably seen digital images.
21 Notice how different the ACR phantom **looks** on a
22 digital image than an x-ray film-screen image. The
23 answer is it doesn't.

24 [Slide.]

25 This is just **so** you can see the ACR

1 phantom really is obsolete for digital images. You
2 can see just about everything in the **ACR** phantom
3 with a digital system, and I gather there are new
4 phantoms. I know there are phantoms under
5 construction, I don't know if any of them have been
6 accepted yet, but I guess this committee is going
7 to have to face those kind of issues as to how to
a test the digital systems.

9 [Slide.]

10 Again, you can see the major difference
11 between film-screen and digital is no difference in
12 terms of if you want to print the digital image or
13 present the digital image the exact same way as the
14 film-screen image, you can do that.

15 [Slide.]

16 The advantage, of course, with the digital
17 image is that you can manipulate the image, and you
18 are not just stuck with what you have got in terms
19 of with a film-screen image, what you get is what
20 you get. You get one shot. If the film isn't
21 exposed properly, you have to do it again.

22 With the digital image, you can manipulate
23 the image, and another advantage for those of **us**
24 who are always looking for magnifying glasses in
25 our divisions, someone in this country is

1 collecting magnifying glasses because I bet if you
2 asked every radiologist in the audience, they are
3 all disappearing from our departments. I don't
4 know where they go.

5 But the joke is going to be on that person
6 because we won't need magnifying glasses. With
7 digital, you just make the image larger, and that
8 is a major advantage just by itself.

9 [Slide.]

10 Now, digital mammography, and D-MIST is
11 going to I think confirm what most of us who have
12 looked at digital and obviously are experienced
13 with film-screen mammography know, and that is that
14 digital mammograms are as good as film-screen
15 mammograms.

16 Are they better? Just by themselves, I
17 don't know. I think there are advantages, and
18 D-MIST may be able to tease that out, we will have
19 to see, but what really makes digital better than
20 film-screen are the things that you can do with
21 digital that you just can't do with film-screen.

22 I am just going to mention three of them
23 today and finish with the one that we are most
24 excited about, which is tomosynthesis.

25 [Slide.]

1 There is a technique called dual energy
2 subtraction. I hope everyone on the committee
3 knows that one **of** the things that we look for on
4 mammograms are calcium deposits.

5 In every mammogram there is probably at
6 least one calcium deposit, so calcium, by itself,
7 doesn't mean a whole lot, but it is patterns of
8 calcium deposition that worry us, and ductal
9 carcinoma in situ frequently will cause the
10 deposition of calcium whether it **is** from dead
11 cancer cells or actual secretion of the calcium.

12 One of the things that we look for on
13 mammograms are so-called clustered calcifications.
14 Well, they are hard to see because these calcium
15 deposits are under a millimeter in size, virtually
16 all the time in cancers, and down around 500
17 microns, that is about a half a millimeter
18 particles, and trying to see them against the
19 background of the very heterogeneous breast
20 parenchyma can be difficult.

21 One **of** the things that the
22 computer-assisted detection units, one of the
23 things that they do well is to find these white
24 spots on the mammogram.

25 There is another approach which is dual

1 energy, which we think will allow us to see them
2 very easily. What is dual energy? Well, you take
3 a high-energy mammogram, and at a high-energy/high
4 kV, the difference between soft tissue attenuation
5 and calcium attenuation is not **as** great as when you
6 do a low kV image, where the calcium attenuation
7 becomes significantly higher.

8 With a computer, if you have taken these
9 basically simultaneously, you can adjust the soft
10 tissue attenuation numbers, so that you change the
11 image, so that the soft tissue in the high kV and
12 low kV image match up exactly, and you can then
13 subtract those, so that there is no soft tissue
14 image left.

15 Because the calcium doesn't subtract
16 exactly with these two changes, then, the
17 calcifications will show up as a separate signal.

18 [Slide.]

19 This is just schematically how this would
20 work. You take a low kV image, you take a high kV
21 image, subtract the two.

22 [Slide.]

23 If it works, the tumor calcifications will
24 stand out and the breast will disappear.

25 [Slide.]

1 This is from an article in the Journal of
2 Radiographics from many years ago where they did
3 this in a chest x-ray. Just to show you, this is
4 the heart and the mediastinum, and the ribs have
5 been subtracted out.

6 [Slide.]

7 That is not quite as impressive as when
8 they subtracted out the heart and mediastinum and
9 left the ribs, and this was done without a scalpel,
10 which is kind of impressive.

11 This is sort of what you can do
12 potentially with dual energy subtraction, and this
13 is a fairly crude subtracted study we think that we
14 can do better.

15 [Slide.]

16 This is a breast tissue sample with high
17 grade ductal carcinoma in situ, that we did a dual
18 energy image with just a standard General Electric
19 digital mammography system, and this isn't just
20 window and leveling, this is actually subtracting
21 out the soft tissue and leaving only the calcium.

22 [Slide.]

23 Here is another one with calcifications
24 from a cancer, and you can imagine if, on a
25 mammogram, when you push the button, you saw

1 nothing but where the calcifications are, that
2 would make the radiologist's search a lot easier
3 for finding calcifications.

4 This is not available on digital systems
5 yet, so you don't have to worry about it yet as the
6 MQSA Committee, but this **is** one of the things that
7 you can do with digital system that really would be
8 next to impossible with a conventional film-screen
9 system.

10 [Slide.]

11 Another sort of corollary to this is
12 digital contrast subtraction angiography. This is
13 a technique that we use all the time in the rest of
14 the body, and now that we have digital detectors
15 for the breast, investigators are starting to look
16 at it in the breast.

17 This is a way of looking at only the
18 vascularity. I think most of **you** know that breast
19 cancers or cancers in general, solid tumors can
20 only grow to a certain size and then they need a
21 blood supply.

22 They can't just continue to grow unless
23 they call in a blood supply, and that is called
24 angiogenesis, a neo-, **a** new vascularity that's
25 developed, and this, of course, **is** one of the areas

1 that people are looking at to try and kill cancers
2 if you can get rid of the blood supply, then, maybe
3 you can kill the cancer, but it is also the way we
4 confine cancers.

5 [Slide.]

6 In magnetic resonance imaging, here, on a
7 CT scan, this is back from the 1980s when Chang in
8 Kansas pointed out that cancers will enhance with
9 iodinated contrast on CT. This is a pre-contrast
10 scan and a post-contrast scan, you can see the
11 cancer has taken up the contrast, and is much more
12 visible with contrast.

13 [Slide.]

14 This is on magnetic resonance imaging,
15 actually, a little cancer that we found in a study.
16 Actually, we were studying her left breast because
17 she had a known cancer there, and we found an
18 unexpected and unsuspecting cancer in the other
19 breast, that was found because it enhanced with
20 contrast because of these new blood vessels that
21 had formed, and this was not visible on a
22 mammogram, ultrasound, we could only see it on MRI
23 and CT.

24 [Slide.]

25 Here is another case, not that one, but a

1 similar one, where we found it on **MRI** and then
2 located it on CT because of the contrast
3 enhancement.

4 [Slide.]

5 Well, this is a potentially powerful tool
6 if we could do it in mammographic, with
7 mammographic resolution. The CT scan doesn't have
8 nearly the resolution that an x-ray mammogram has,
9 and so if we could take the advantage **of** seeing
10 small blood vessels at high resolution, we may have
11 a very powerful tool.

12 [Slide.]

13 **So**, again schematically, we would do a
14 pre-contrast mammogram--this is before injecting
15 any contrast--then, intravenous administration of
16 iodinated contrast. This is the same material that
17 is used every day in departments for CT scans and
18 just about anything that we **do** that needs what are
19 called contrast agents. It is generally iodine.

20 Then, you subtract the pre- and
21 post-contrast, and the only thing that is left
22 after subtracting is the vascularity, and in this
23 nice schematic, it works beautifully.

24 [Slide.]

25 This is an animal model that we did a

1 lumber of years ago. This is bone. There is a
2 tumor that has been implanted right here. It is a
3 tittle hard to see because we haven't done the
4 subtraction.

5 [Slide.]

6 When you do the subtraction, now you can
7 actually see the nest of blood vessels that has
8 developed around this tumor. This was done with a
9 digital mammography detector, so that the spatial
10 resolution is quite exciting.

11 [Slide.]

12 Other folks are now looking at this in the
13 human breast. Martin Yaffe and his group up at the
14 University of Toronto, using the Fischer system,
15 has shown contrast enhancement **of** a cancer, and
16 just as we can with magnetic resonance, they can
17 track the contrast as it flows through the tumor,
18 so as the contrast gets to the tumor, there is a
19 sudden increase in contrast in the tumor.

20 Some of the contrast actually leaks out,
21 so it stays in the tumor, so the tumor contrast
22 stays high, but some of it leaks out, and this is a
23 fairly characteristic curve for a cancer, which
24 this turned out to be.

25 We have seen this on magnetic resonance.

1 We should be able to do this less expensively and
2 at higher resolution with iodine and digital
3 mammography.

4 [Slide.]

5 John Lewin has also done some work in this
6 and loaned me these slides, where he is dealing
7 with the issue of registering these images.

8 One of the big problems that the
9 radiologists and physicists in the audience know
10 about is to do accurate subtraction, where you
11 subtract one image from another, they have to line
12 up perfectly, otherwise, you get all kinds of
13 artifacts.

14 John has taken another approach where he
15 takes a high-energy image and then a low-energy
16 image, and subtracts them, and that can be done
17 very quickly, just like the calcium that I just
18 showed you.

19 That leaves the iodine, which blocks
20 x-rays at much greater rate than soft tissue, so
21 then you can have the iodine image, if you will, of
22 the cancer left behind.

23 [Slide.]

24 Here is just another case that John gave
25 me, sort of a subtle lesion, and then much more

1 obvious following the contrast.

2 [Slide.]

3 Now, what I was sort of asked to talk
4 about today is a technique that we are developing
5 at Mass. General, and I should issue the disclosure
6 that I am, number one, biased because this was our
7 idea for the breast and we hold patents at Mass.
8 General on it, so that I am not totally objective,
9 although I will try to be as objective as I can
10 here.

11 Three-dimensional digital mammography, I
12 think is going to be the first technique that
13 really sets digital mammography off from
14 conventional film-screen, and there are a lot of
15 advantages that I will show you.

16 [Slide.1

17 What do I mean by 3-dimensional
18 mammography? Well, there is a technique that was
19 actually written about back in the late 60s, early
20 70s, called tomosynthesis. What is tomosynthesis?

21 In conventional x-ray--and we will talk
22 about mammography, which is an x-ray
23 technology--the breast is between the x-ray beam
24 and the detector, and x-rays come through the
25 entire structure of the breast, and something that

1 is in this plane, superimposes on something that is
2 in this plane, and they project on top of one
3 another on the mammogram.

4 One of the challenges that radiologists
5 face is to try to separate the structures that are
6 overlapping, and one of the reasons we take views
7 from the side and from top to bottom is to help the
8 radiologist understand the 3-dimensional location
9 of structures, so that we are not fooled by
10 overlapping structures.

11 I should tell you, though, that in our
12 practice, and Ed Sickles, I was talking with Ed,
13 and he has the same experience at the University of
14 California at San Francisco, about 25 percent of
15 the women that we recall because we think there is
16 a problem on their mammogram, are recalled because
17 of overlapping structures. It turns out to be
18 nothing, but the radiologist, just looking at the
19 two films, can't be sure of that, and so the
20 patients are recalled.

21 [Slide.]

22 Now, this just an example of a very subtle
23 tumor. It is not so subtle because we have got a
24 spot compression panel on it, and I wanted you to
25 be able to see it. Here, you can see a spiculated,

1 fairly high-density mass that is partially hidden
2 because of the rest of the breast, the normal
3 breast structures.

4 [Slide.]

5 Now, once this is taken out at surgery,
6 this is following needle localization, it is easy
7 to see. Why is it easy to see? Well, first of
8 all, it is a thinner structure, and so there is
9 less scatter, and so on, but we have taken away
10 what is called the structure noise of the breast,
11 which is what is in front of it and behind it on
12 the mammogram.

13 [Slide.]

14 I liken that to looking for a birch tree
15 in a pine forest, couldn't find a birch tree in a
16 pine forest, but this is a deciduous, but it is
17 close anyhow. Here is the birch tree. It is
18 pretty easy, everyone can see it. It is white, it
19 stands out against the green background.

20 But as you start walking along--I had to
21 go all the way to Norway to do this, by the way, it
22 was a tough experience, but I did--as you walk
23 along, it starts getting hidden, and after a while
24 you really can just barely see the birch tree, if
25 at all.

1 [Slide.]

2 Here, my diagram of a birch tree in a pine
3 forest, it is very hard to see the birch tree even
4 if it were just one row back behind these pine
5 trees. Well, how does this compare to the breast?

6 The breast, you all know about dense
7 breast tissue. Dense breast tissue are the
8 fibroglandular structures, principally the fibrous
9 structures although the glandular tissue is also
10 dense, that are highly attenuating of the x-ray
11 beam, and cancers have very similar x-ray
12 attenuation to fibroconnective tissue.

13 *So*, it is sometimes very hard and
14 often--not often--but not infrequently impossible
15 to differentiate a cancer from the normal tissue,
16 and this is the reason why cancers don't show up on
17 mammogram. They are hidden by the dense tissues.

18 This can happen at any age, and the
19 density of the breast, just as a quick aside, has
20 nothing to do with how firm it feels on clinical
21 breast exam. The density is an x-ray attenuation
22 phenomenon, you can only tell density by doing a
23 mammogram, and the density changes gradually with
24 increasing age. It is nothing that happens at
25 menopause or age 50, as we have been led to

1 believe.

2 Women at age 30, about 90 percent of them
3 have dense breast tissue, and that changes by about
4 1 to 2 percent with each increasing year of age, so
5 that the percent of women with fatty breast
6 increases. Fat is like window glass or having a
7 birch tree out in the middle of a field. The
8 density of the breast is like the pine trees.

9 [Slide.]

10 So, if we could just get rid of the pine
11 trees without having the environmentalists against
12 us here, we would be able to see the birch trees.

13 [Slide.]

14 So, the trick really is to make slices
15 through the breast, and I think many of you are
16 probably familiar with CT scans, which make slices
17 through the breast tissue--again, the radiologists
18 are all well familiar with cross-sectional
19 imaging--and what that does is it gets rid of what
20 is in front and what is in back, so that you can
21 see the birch trees.

22 [Slide.]

23 Well, how can you do this in the breast?
24 In the days when I was very young, we used to move
25 the x-ray tube in one direction, and the detector,

1 in this case it was film, in the other direction,
2 and they would move in tandem, and you can probably
3 imagine that as you move the x-ray tube in one
4 direction and the detector in the other direction,
5 only the things that are at the fulcrum of the
6 motion will not look like they are moving,
7 everything else will look blurred. I will come
8 back to that in a minute.

9 But this is the old way of doing
10 conventional tomography, move the tube in one
11 direction, the detector in the other, and you could
12 blur everything but the plane that you were
13 interested in. If we were doing this in the
14 breast, it would be in the breast.

15 The problem with this is for every slice
16 that you want to make through the tissue, you have
17 to repeat this sequence at full dose. So, to go
18 through the breast, say, get 60 slices through the
19 breast, would require 60 mammographic exposures.
20 Clearly, we are not going to do that, so this
21 approach to making slices through the breast isn't
22 going to work.

23 [Slide.]

24 It turns out that using a computer, you
25 can move the x-ray tube through an arc, and what we

1 do in our system is move the x-ray tube through an
2 arc of 50 degrees. That is just what we started
3 with. We think that there are better arcs to
4 choose.

5 We are moving it through 50 degrees, and
6 as we move it, it is stopping and taking a picture
7 11 times from 11 different angles. We can do that
8 in 7 seconds. The breast stays stationary and the
9 detector doesn't move, so the breast and the
10 detector are stationary, just like a conventional
11 mammogram.

12 It takes a little bit longer. It takes 7
13 seconds as opposed to conventional mammogram is
14 anywhere from half a second to a couple of seconds,
15 and we take 11 images. You say, well, gee, that
16 must be a lot of dose.

17 Each individual image is a fraction of the
18 total x-ray dose of a film mammogram or, for that
19 matter, a digital mammogram at the same dose. So,
20 the dose for these 11 images adds up to about 1.5
21 film-screen mammogram exposures, so the dose is
22 actually less than the tubular mammogram.

23 [Slide.]

24 Now, why are we doing this? Well, if you
25 look at again our objects that are in the breast

1 here, when we take a conventional x-ray, they are
2 lined up and they are hard to tell apart.

3 As we move the x-ray tube through an
4 angle, you can see--and I will do this back again,
5 so you can see it--that at different angles,
6 something in one plane moves differently than
7 something in the other plane.

8 Again, we move through the angles, and if
9 you watch, the structures start moving apart. That
10 is called parallax, and if you close one eye and
11 point to an object on the wall, and then change,
12 your eyes closed, the first eye, and open the other
13 eye, you will see the object seems to shift. That
14 is because your eyes are looking at it from a
15 different angle, and it is that shift that is
16 called parallax.

17 [Slide.]

18 We can take advantage of that with
19 tomosynthesis to make slices through the breast,
20 because we can then take these images that we have
21 put together, and line them up, and this is why we
22 need digital systems because you really can't do
23 this certainly efficiently with film images. You
24 need a computer image, it is much easier.

25 [Slide.]

1 Here, in the synthesized images, now the
2 spiculated, the irregular abnormality, or anything
3 in that plane will register on all the images. The
4 other ones won't because they are in a different
5 location. They will misregister and you will have
6 blurring by the misregistration.

7 Now, let's say we wanted to see the plane
8 that had this irregular shape in it. Well, we just
9 shift the images and add them again, and now what
10 is in the plane of the irregular shape adds up and
11 is sharply defined, and everything else is
12 misregistered. That is called tomosynthesis, that
13 was named tomosynthesis.

14 [Slide.]

15 Well, we have taken it several steps
16 beyond now. We don't do that so-called shift and
17 add, but we accomplish the same thing, and this is
18 just to acknowledge the people that we have worked
19 with from Brandeis University to develop advanced
20 algorithms, and I have to tell you that this was
21 done under a grant from the Army.

22 [Slide.]

23 General Electric built the machine for us,
24 and basically, the x-ray tube moves up in this
25 housing. This is just here so we don't whack the

1 patient in the head as the x-ray tube moves, but it
2 is a standard digital mammography system, digital
3 detector right here, compression system. This just
4 has to do with counterbalancing the movement of the
5 x-ray tube.

6 Again, this is a prototype and not as
7 elegant as a finished system would be, but to the
8 patient, it is like having a mammogram. Now, I
9 will say just quickly as an aside, we are
10 collecting data to see if we can reduce the
11 compression needed for doing mammography. I know
12 most women don't care much about that, but we would
13 like to reduce the amount of compression that is
14 needed.

15 We are not sure we can get away with that.
16 Right now we are using the standard mammographic
17 compression, but another advantage of tomosynthesis
18 will be that we think we can just do one
19 compression, that we won't need to do the two
20 projections because, as I will show you, we will
21 have 3- dimensional information.

22 So, the x-ray tube moves up here. The
23 exposure, as I say, takes 7 seconds. I think we
24 have had one case out of over 250 that we have done
25 where we think there was some movement by the

1 patient, but they seem to be okay, and again, 11
2 images in 7 seconds for 1.5 film-screen dose, not
3 film-screen study, but film-screen image.

4 [Slide.]

5 Now, it is not going to be great here in
6 this room because the lighting isn't terrific, and
7 I will also give you the caveat that this looks
8 much better on a workstation which is designed for
9 this, but here is a conventional film-screen
10 mammogram, and I am sure all the radiologists
11 picked out this cancer. Actually, it is a very
12 subtle cancer.

13 I think we picked it up because there is
14 some calcium that just happened to be nearby and
15 drew the radiologist's eye. This is a very subtle
16 lesion.

17 [Slide.]

18 Here it is up close, a little better, but
19 you can see you have got all the structure noise of
20 the breast that is 'getting in the way.

21 [Slide.]

22 Here it is from the cranio-caudal
23 projection, again pretty subtle.

24 [Slide.]

25 Even when you get up close, it is still

1 pretty subtle.

2 [Slide.]

3 This is the tomosynthesis image, and, of
4 course, it takes getting used to. What I am going
5 to do, we are going to be paging through. We have
6 reconstructed this at 1-millimeter thick slices.

7 We actually can go down to--we have done
8 half-millimeter, we can go to thinner, it just
9 requires much greater computer calculations.

10 That is right now the rate-limiting step.
11 It takes about two hours to process one of these
12 images. That cuts your throughput down a little
13 bit, but we know how to do it actually within a
14 minute or two, so that is really more the
15 computational power, and computers get cheaper and
16 cheaper by the second, so that is not an issue.

17 [Slide.]

18 Now, what I am going to do is just page
19 through, and we are starting to move into the
20 breast, and you will start seeing structures. I am
21 going to stop it here. You can start seeing
22 Cooper's ligaments coming into view, these curved
23 lines.

24 [Slide.]

25 If you watch right here--it is hard here

1 to stop and start with Powerpoint--but now you can
2 see the cancer without the noise **of** the breast in
3 the way. I will show you this up close in a
4 second. Then, we will page through the cancer and
5 out to the other side.

6 [Slide.]

7 Just to show you, this is a little easier
8 to appreciate, these are the blood vessels just
9 under the skin **on** the other side. Notice that we
10 just saw them at the end of the paging through,
11 because they are not in the slices that preceded
12 them.

13 [Slide.]

14 Let me just show you this up close.
15 Again, on a workstation, it is much easier to deal
16 with this. Here we go, just looking at the tumor.
17 Now you can see I think with much greater
18 sharpness, the spiculations **of** the lesion, its
19 irregular margins, and just the conspicuity of it.

20 [Slide.]

21 We will go to the next. I tried to put
22 them side to side, and adjust them the same. This
23 is the conventional mammogram on the left. Here is
24 the tomosynthesis on the right. I think the
25 ability to see this tumor is much greater than

1 trying to pick it out of the background there.

2 [Slide.]

3 Here is another patient. This was a great
4 pickup by one of my associates. There is some
5 funny architecture right in here. It is actually
6 not this, it is up in here. Let me see close up.
7 You can see there is some funny--again, the
8 radiologists I think can appreciate some funny
9 architecture there, everyone else is going what is
10 he talking about. Anyhow, this is a good pickup.

11 [Slide.]

12 Here, in just the projection, I am going
13 to show you in this area, I don't even think I see
14 it on the conventional mammogram, but anyhow, here
15 is the tomosynthesis. I think you can now see
16 pretty easily the spicules coming out of this
17 tumor, and then somewhat to our surprise, here is a
18 second lesion.

19 To get into our study, you have to have an
20 abnormality on the film-screen image to begin with,
21 so that this is tying tomosynthesis one hand behind
22 its back, but this we have had now three cases
23 where we picked up a lesion that was not visible on
24 the conventional mammograms. We actually thought
25 there might be a third one up here, but the surgeon