

1 If you had a five-out-of-five rating, what
2 you did with the zero, one, two, three, four out of
3 fives whether you included those or not as false
4 positives would change the median false marker rate
5 but it's on the order of two or three per case.

6 In the final column we see that this is a
7 range of the diameter to those true positives. You
8 can see that it ranges from about eight to nine. For
9 the less than three out of five it was 7.4. For three
10 out of five it jumped up to about 11 and fell down to
11 seven again. The idea of this column is just to show
12 there doesn't really seem to be a bias associated with
13 how large the lesion was based on how they rated it as
14 classic or not.

15 Just as a final summary, if there was less
16 than three out of five panelists, there was
17 approximately 65 findings and the sensitivity was
18 about 32 percent. If it was greater than three out of
19 five, there was about 77 findings. This is about half
20 and half -- relatively close to half and half for the
21 data set. The sensitivity jumped up to about 81
22 percent.

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1 So just in summary for the CAD stand-alone
2 performance, what was found by the sponsor was there
3 was a large variation in performance of the CAD based
4 on the physician's assessment of the nodule's
5 appearance as classic. Whether it was classic or not
6 would make a big difference on how well the CAD
7 performed.

8 Just a note, generally the CAD -- the
9 sponsors talked about the CAD being associated with
10 these discrete spherical types of lesions and not
11 necessarily some of the other types of lesions that
12 were potentially marked.

13 So just in summary for this part of the
14 presentation, what the sponsor found was that the --
15 what we found was that the Az was an appropriate test
16 statistic for the clinical analysis and this was based
17 on the fact that there was no substantial crossing of
18 the pre and post-CAD ROC curves.

19 The primary analysis, this was based on a
20 fixed three-member expert panel. It showed a
21 statistically significant Az improvement in the
22 detection with the CAD. What was also found was the

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1 ANOVA-after-jackknife and bootstrap showed comparable
2 significance testing and confidence intervals.

3 The secondary analysis, this was with a
4 variable number of panel members where the sponsor
5 varied the number of panel members. They also varied
6 the panel makeup using a bootstrap selection of the
7 panel members so this is a random panel mix now. This
8 confirms statistically significant Az improvement in
9 the detection with CAD.

10 Then, finally, for this CAD stand-alone
11 performance what was found was that there was a large
12 variation in CAD performance based on the reassessment
13 of the nodule's appearance. A more general conclusion
14 from stand-alone performances is that this type of
15 analysis is necessary for appropriate utilization of
16 the device by the clinicians in the field and for
17 potentially reassessment of future algorithm
18 revisions.

19 Now I'll turn it over to Dr. Sacks again
20 to make some conclusions.

21 DR. SACKS: Okay. I want to then draw
22 some clinical conclusions about this statistically

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1 significant gain. Granting the statistical
2 significance of a gain in Az of .02, what is the
3 clinical significance and this is a point that was
4 discussed somewhat this morning.

5 Let me recall for you an earlier slide
6 that I have excerpted this from. That is, that the
7 clinical utility of this device is that the CAD is
8 intended to reduce the number of missed nodules. That
9 is, it is intended to increase the user's sensitivity,
10 not increase the area under the curve, although that
11 is related.

12 A gain of .02 in Az understates the
13 relative gain in sensitivity. Why is that? When the
14 CAD is used according to instructions to retain all
15 judgments of actionability, even if unmarked by the
16 CAD, the user always necessarily maintains or
17 increases his or her sensitivity and, indeed, always
18 maintains or increases the false positive fraction as
19 well. They both have to go up. They could stay the
20 same but that would be an extreme case that wouldn't
21 likely happen, but they cannot go down either one.

22 What that means in ROC space is that --

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1 let me walk you through this slide -- the blue curve
2 is intended to be a representation of the unaided
3 initial reading. The red curve is the aided reading.

4 We've been talking about the difference in area
5 between under the red curve and under the blue curve.

6 But if you talk about a particular
7 operating point on the blue curve unaided and ask what
8 happens when you use the CAD, you move to some point
9 on the red curve and if you obey those instructions
10 not to back off when the CAD fails to mark something
11 that you thought was actionable, you necessarily move
12 up and to the right somewhere in that quadrant such as
13 this arrow here so you move to some point here.

14 Now, Dave Miller showed you a number of
15 representative arrows if you were to use a particular
16 point on the rating scale on the blue curve and keep
17 that same point on the rating curve -- on the red
18 curve, the same rating, 80 or 50 or 20.

19 The problem is that radiologists while
20 they could read by assigning a number to a study and
21 always obeying a preset range for themselves saying,
22 "If I assign any case 70 or more, then I am always

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1 going to act on it the same way.

2 If I assign between 40 and 70, I'm always
3 going to act on it the same way. If I assign under
4 40, I'm always going to act on it in the same way,"
5 then those points might be relevant. Radiologists
6 could do that but I'm a radiologist and I can tell you
7 radiologists don't do that.

8 What they do do is they look at a case and
9 they decide, "Do I act on this or do I not?" Or if
10 there is a trichotomy such as in mammography where
11 there is biopsy or short-term follow-up or return in a
12 year for screening, that is the decision you make.
13 That gives you an operating point that may or may not
14 lie on the curve that you would construct if you gave
15 a rating.

16 It wouldn't necessarily lie on that curve.

17 It would lie on that curve if you always assigned
18 your action based on a preset fixed range of ratings.

19 But because those are done independently, those modes
20 of thinking, the point that you operate on in terms of
21 actual sensitivity and specificity may or may not lie
22 on the ROC curve.

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1 For this particular clinical study we
2 don't know but what we do know is if you maintain that
3 rule, and you are free to violate it if you are going
4 to, but in this clinical study people did not violate
5 it and what we can see is if we put this in the
6 labeling and say to potential users out there, "Stick
7 with this rule and you are not going to lose
8 sensitivity," then what you're going to be doing is
9 moving up and to the right.

10 And you can see from this gain in
11 sensitivity, this increment here which is along -- TPR
12 is just true positive rate or fraction. It's just
13 another word for sensitivity -- that increase is a
14 little more impressive than .02. I can't quantify it
15 but you can expect that your gain in sensitivity is
16 going to be greater. The utility of knowing that the
17 red curve is higher than the blue is that you know
18 that you're not so greatly increasing your false
19 positive rate as the fall to a lower curve.

20 Now, here is an example. For example, if
21 I start here and I maintain that rule, I'll go up and
22 to the right but if I don't, I could fall even though

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1 I'm going to a higher curve from blue to red. Those
2 are the same two curves as in the previous slide.
3 Nevertheless, I could drop my sensitivity if I don't
4 follow that instruction.

5 So any statistically significant
6 improvement in Az means an even greater relative gain
7 in sensitivity and one achieved without falling to a
8 lower ROC curve if the reader maintains that rule not
9 to back off if the CAD fails to mark something that he
10 or she thought was actionable to begin with.

11 Now, another point. The real question for
12 judging the safety and effectiveness of any device is
13 how does its introduction into general use compare to
14 what we have today where it doesn't exist? The same
15 question applies to a CAD.

16 Can we infer from the fact that there was
17 an improvement in the average user performance
18 measured in terms of Az in a clinical study that the
19 average user will improve his or her performance,
20 again measured in terms of Az, with the CAD in
21 clinical practice.

22 That is, improve over his or her current

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1 clinical performance which is in the absence of any
2 CAD for miles around. To put it another way, is the
3 unaided reading in a clinical study a good surrogate
4 for current CADless clinical practice?

5 What I'm showing here is let's suppose it
6 is a good surrogate. Current clinical practice may
7 have a CADless reading Az somewhere here along some Az
8 scale. In a clinical study if the unaided reading is
9 a good surrogate for that, then the fact that the
10 aided reading is higher than the unaided reading, then
11 the aided reading is also higher than current CADless
12 clinical practice.

13 But, for example, in actual clinical
14 practice with CAD, that is, in the future, the unaided
15 Az could be lowered potentially by failure to read
16 first as one would normally read. That is, with
17 adequate vigilance. If this were to happen, then the
18 aided Az could also be lower than the current CADless
19 practice. And to show that in a diagram, in other
20 words, if this aided reading had an Az that was
21 significantly lower than the Az in current clinical
22 practice, it could pull down with it the aided reading

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1 so that it was below your current practice.

2 In order to avoid that, well, what would
3 be the implications of such lowering of vigilance for
4 judging the safety and effectiveness of the CAD? Can
5 labeling help prevent this? Labeling issues. Two
6 rules if followed by CAD users in future clinical
7 practice with the CAD will help prevent missing more
8 nodules than former reading without a CAD.

9 The first rule is an always rule. Always
10 read unaided first and as carefully as if you had no
11 CAD. This would help keep the Az of the aided reading
12 higher than the Az of the current CADless reading. We
13 can't make users of this follow these instructions but
14 we can guarantee that it's in the labeling.

15 Secondly, the never rule. Never back off
16 from unaided judgment of actionability of a nodule if
17 the CAD fails to mark it. This would prevent the
18 sensitivity from falling below that of current CADless
19 sensitivity. That is, it would prevent the
20 radiologist from missing more rather than fewer
21 nodules.

22 DR. IBBOTT: Thank you. At this point Dr.

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1 Wagner has a short presentation to make.

2 DR. WAGNER: Yes. This is just a trivial
3 comment but it is along the lines, I think, of where
4 Bill Sacks was going just a moment ago. The number
5 .024 may sound small and he showed how it may have a
6 bigger impact than that small number sounds.

7 If you do an area under the ROC curve here
8 is the good stuff, .85. Here is the bad stuff, .15 or
9 .12 or whatever. That .024 is also the correction
10 improving the false negative piece and all the
11 inference that was done on the area under the curve
12 difference because it's just a difference between one.

13 Here is the curve and here is the area under and here
14 is the difference. The difference is just one minus
15 everything else we've been discussing today.

16 The statistics of one minus something are
17 the same as the statistics of that something so the
18 area under the curve is also the reduction in false
19 negatives with all the statistics in there averaged
20 over all the false positive rate so that is another
21 interpretation of that.

22 So .024 may not sound like a lot compared

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1 to .86 or something like that, but it also is to be
2 compared to .15 or .14 or whatever the missing piece
3 is. All the statistics if you consider them tight for
4 the previous part, it's the same statistics. I don't
5 know if that helps but .024 looks a lot better
6 compared to .12 or .13 than it does to .85. That is
7 statistically robust. Thank you.

8 DR. IBBOTT: Thank you. Before we go onto
9 the lead reviewers, I'll take a moment to see if
10 people have any questions of these recent speakers,
11 particularly questions in the nature of clarification
12 again before we get onto the real discussion later.

13 Yes, Elizabeth.

14 DR. KRUPINSKI: Can you clarify or explain
15 without getting into all the gory mathematical details
16 when you go from looking at quadrants, then the Az is
17 based on patient. For example, suppose you've got
18 your four quadrants and you've got a true positive
19 here, a false negative here, a false positive here,
20 and a true negative here as quadrants. When you then
21 go to Az on a patient, is that patient true positive,
22 false negative, false positive, or some weighted

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1 combination there? Anybody who knows the answer.

2 MR. MILLER: I think it's a quick answer.

3 So when you compute the Az all four quadrants are in
4 there for computing the Az but that is to compute it
5 originally. Then when you do the jackknife you pull
6 out all four quadrants so, therefore, the jackknifed
7 Az, which is the unit of analysis for the ANOVA, is
8 based on the case because you pulled out the four
9 quadrants together.

10 But when you compute the Az, you do have
11 each of the four quadrant ratings compared against
12 each of the four quadrant truths. This is discussed
13 in Nancy Obuchowski's paper from Biometrics in '95. I
14 ran those programs as well as the ones that we did
15 just to make sure that we were getting the same
16 estimates.

17 DR. KRUPINSKI: So all decisions are
18 preserved basically.

19 MR. MILLER: All decisions are preserved.

20 DR. IBBOTT: All right. Then we will now
21 have some brief presentations by the panel's lead
22 clinical reviewer, Dr. David Stark, and the lead

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1 statistical reviewer, Dr. Brent Blumenstein.

2 Dr. Stark.

3 DR. STARK: Thank you. I would like to
4 begin by congratulating the applicant, the industry in
5 general, the FDA staff, and the panelists. This
6 discussion and the record of it, I think, documents
7 substantial progress that's been made in the
8 methodology for research and product development in
9 this field of computer-aided diagnosis or detection
10 and, frankly, the verification of these results so
11 that we can apportion resources responsibly and
12 regulate and improve overall quality of clinical care.

13 As is noted in what I've read from the
14 FDA's notes from last year, in particular, this
15 application, this issue, is a very prodigious task and
16 the technology is quite similar to really more to
17 putting the Spirit and Opportunity on Mars than most
18 other things that we clinicians face or have
19 historically faced in our training in how to decide
20 how to care for patients.

21 Nothing really could be further from the
22 way a surgeon decides whether they are going to start

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1 doing laparoscopic cholecystectomies without any review
2 or oversight as opposed to exploratory laparotomies.
3 I'm a little bit concerned about the fastidiousness
4 and the zeal with which we are putting -- are
5 obsessed with technology. I'm assessed with
6 technology.

7 Some of the panelist here are devotees of
8 little PDAs like I am and things but there are many
9 red herrings here. There are many unintended
10 consequences and this is an extremely important task
11 we have in front of us, not to move too quickly and
12 not to move too slowly.

13 I just want to remind everybody that with
14 those two space landers, spaceships that we've been
15 following with our families and children, the
16 unintended consequences for something that is manmade
17 and simply mechanical like an overheated solar panel
18 or a flash memory that's choked with data, this is
19 more complicated than the Challenger accident or
20 putting Spirit and Opportunity on the moon in my
21 humble submission.

22 That is because we are limited. We chose

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1 to go into biology but there are enormous biological
2 variations here. Even as a group I doubt we have the
3 collective wisdom and strength to recognize all of
4 them given the time that we've had.

5 There are numerous coincidental clinical
6 issues and this panel has focused largely on what I
7 believe is a red herring of the statistic of Az. I
8 implore people not to think that just because we can
9 launch a bottle rocket we can reach the moon.

10 My own papers which I have cited to the
11 committee have shown a larger and more convincing
12 increase in the detection of liver metastases with
13 magnetic resonance imaging using exactly this same
14 methodology with some of the same authors and we were
15 wrong because of some of the issues that have been
16 raised here today.

17 A statistically significant phenomenon in
18 the laboratory with all of these little nuisances
19 tearing and pulling at it, and these are only a
20 fraction of the issues, can give us the enthusiasm
21 that we can reach the moon but there will be problems
22 with insulation flying off rockets and things like

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1 that. The unintended consequences are what I'm
2 concerned about as we talk about safety and efficacy.

3 First about some of the red herrings. The
4 burden of the 300 scans, it is a burden to have to
5 look at so many images but that's a bit of a myth.
6 One of the ways that we have improved our efficiency
7 as radiologists in reading these images is we no
8 longer tile them.

9 We melt through a stack with a trackball
10 so the soft film reading to a certain extent mitigates
11 the number of scans. It really doesn't matter if you
12 have 50 or 500 to a large degree if you are
13 trackballing through a stack.

14 Furthermore, this product doesn't address
15 that issue because it really is largely asking the
16 radiologist to still do his conventional work and then
17 add additional readings to it, albeit slice by slice
18 computer selected.

19 The problem that we're here to face, to
20 solve, and the industry is trying to address, as the
21 physicians are, is that we have a false negative rate
22 in detecting nodules in the lungs that is unacceptable

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1 to clinicians, to the public, and to healthcare
2 providers and those who fund it.

3 This study population does not reflect the
4 fact that the false negative rate of 24 percent is a
5 number we've all been, I think, using by assent here
6 today but it's different depending on the study group,
7 I'm sure. That might be plus or minus 10 percent, 15
8 percent easily.

9 But that's 24 percent of one in 100 that's
10 positive. The radiologist faces 99 negative scans for
11 every one that he has to find. These study conditions
12 the radiologists faced two out of three were positive
13 and positive perhaps in multiple quadrants.

14 The false positive fraction, which is
15 quite large here, is over a very large denominator.
16 99 out of those 100 patients who have truly negative
17 scans will bear the burden of the false positives, the
18 patients and the radiologists caring for them.

19 The question of efficacy can be as simple
20 as if we assume the radiologist is perfect and just
21 plays by the rules and adds no false positives, then
22 he has the ability perhaps to improve his false

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1 negative rate which is embarrassing but it's the state
2 of the art of medicine from perhaps 24 percent or
3 worse to perhaps 10 percent better. Still horribly
4 embarrassing so we have some meager pickings and still
5 an unacceptable result, I think, from a final
6 objective. Nonetheless, a step in the right direction
7 would be a step in that direction.

8 The false positives, though, while I
9 believe we do have in one of the curves, I think it's
10 figure 11 on page 53 in one of the two studies, did
11 show some degradation of performance where the
12 radiologist somehow managed to not be perfect and to
13 eliminate all the false positives which is
14 unbelievable that they can do that.

15 I believe some radiologists are going to
16 be induced to call things positive. It's just not
17 realistic that another look when you are prompted to
18 ask you are going to cause some more false positives
19 and there is the possibility of degradation with
20 scatter around the ROC curve. These will whether they
21 are due to distraction error, there will be, maybe
22 unmeasurable, but as happens in medicine unnecessary

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1 biopsies.

2 Dr. Castellino talked about the effect on
3 treatment if you call five lesions instead of three.
4 Some surgeons will say, "I won't operate on three
5 pulmonary nodules and do a metastasectomy. I will go
6 to chemotherapy." Or if there's two. One pulmonary
7 nodule, we'll excise it out. If there's two and it's
8 a false positive, no chemotherapy. Unilateral versus
9 bilateral disease, no surgery.

10 So the consequences of a mistake, a false
11 positive is huge because they add to that minority,
12 that one in 100. And there are, of course, the
13 complications of follow-up CT scans with or without
14 contrast. I'll get to contrast media later. We
15 haven't discussed it today but one of the claims is
16 that this is effective with or without contrast media
17 but we haven't seen, I believe, data on that point.

18 So one of my concerns is the nonclinical
19 circumstances in terms of the patient mix, the
20 circumstances of the readers. We had at least one
21 reader who read 90 cases in a day. There were more
22 than one. They may have been exceptionally strong

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1 readers but we know they weren't reading under
2 clinical conditions. They were ignoring many of the
3 things that radiologists are obligated to worry about.

4 Radiologists are not limited in their
5 obligation to work with this machine. They have to
6 look at the neck and look at the spine, look at the
7 ribs, look at the chest wall, look at the abdomen, and
8 look at the adrenal glands, especially for lung
9 cancer.

10 So these radiologists in this study had a
11 very, very narrow task in front of them not even
12 looking at the pulmonary vessels or the mediastinum.
13 Not even looking at lymphodes. They were just looking
14 at airspace for nodules abutting airspaces trying to
15 match the technology.

16 This technology forces the radiologist, in
17 effect, to work for it even though we insist the
18 radiologist first do his own job. He then has to come
19 back, read in a skewed way, and correct the numerous
20 false positives, protect the patient from the numerous
21 three per study false positives that this technology
22 causes.

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1 Now, I'm ignoring cost in this analysis.
2 I've been instructed that effectiveness here comes at
3 any cost so I'll leave that for other people to
4 address that but there are still risks because the
5 radiologist has a certain amount of time and he is
6 going to make mistakes.

7 The fast readings may have, as we've heard
8 from the statisticians, made this very small, though
9 statistically significant. Increase in Az may make it
10 evaporate. I submit that even a larger Az, my own
11 papers have shown, is often not clinically significant
12 for the enumerable reasons that we've touched upon,
13 albeit quickly, because we've mostly spent our time on
14 the red herring on ROC methodology. Red herring for a
15 decision today, I believe, but extremely important for
16 the future of this technology.

17 If we do move on to the next phase and
18 improve this product, I did not see that it calls for
19 significant training of the radiologists. I think the
20 warnings that will be given to the radiologists are
21 limited and I think the temptation and the ability to
22 misuse the product is significant.

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1 I think that very significant discussion,
2 or substantial discussion interaction with the FDA
3 about what would be appropriate warnings and training
4 and, importantly, post-market surveillance to see how
5 this actually performs with realistic clinical
6 readings, not in the unrealistic setting that here was
7 designed to feed an ROC study.

8 These radiologists who were safe here were
9 diligent, paid, and focused on eliminating this false
10 positive rate. They did not have to deal with
11 coincident chronic obstructive pulmonary disease,
12 artifacts from patients having the arms by their side.

13 Contrast agent given in large boluses which can cause
14 artifacts, change the appearance of the blood vessels
15 throughout the lungs.

16 We didn't discuss how the algorithm
17 operates. It sounds to me much like it does not use a
18 maximum intensity projection. It does not identify
19 the vessels per se. It's really looking at ovoid
20 intrusions on airspace. Product development is not --
21 I don't have enough information to comment further.

22 Let me see if I have more from my notes

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1 and I'll try to wrap up. Well, I've been asked to
2 state my views and I hope it's clear that I am
3 sincerely impressed with the progress that has been
4 made but I think this is an extremely ambiguous and
5 complex project and I am really worried about the real
6 world pressures on the radiologists in that I don't
7 think -- I do not believe that we have shown that we
8 have effectively -- that we have demonstrated
9 effectiveness in that -- effectiveness can come in two
10 ways.

11 Either improving our accuracy and assuming
12 that we show that we do not increase the false
13 positive rate and that we can effect significantly in
14 a clinical setting the 24 percent false negative rate
15 for real lesions. I think there is evidence there
16 that it's going in the right direction but I really am
17 not persuaded that we are looking at much more than a
18 statistical trend that because of the way the study
19 was conducted statistically reached significance for
20 the ROC.

21 The other way to reach effectiveness would
22 be to improve the efficiency of the radiologist

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1 working so the radiologist would have time to read
2 more carefully. I really do believe that a careful
3 re-read or a second read of these scans might be more
4 effective, accurate, and efficient than the use of
5 this modality.

6 I believe that we need a placebo study.
7 There is no placebo study where we see the effect of
8 simply introducing the random false positives in a
9 population that is 99 percent negative and see if we
10 do any better at finding that one in 100 who has a
11 true positive.

12 I believe this is such a statistically
13 based application and we have such a skewed set of
14 circumstances for collecting the data, the data set
15 that we looked at, the way the examinations were done
16 and the very narrow statistic analysis that was done
17 that I do think we have to look at the history of the
18 ROC which is unproven that a p-value for an ROC should
19 justify as proof sufficient effectiveness for FDA
20 approval.

21 And in terms of safety ignoring cost, I
22 think that we have seen in at least one of the graphs

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1 provided that there is possible degradation. We have
2 an intuitive understanding that there is possible
3 degradation and I have no doubt this product will help
4 some patients but I think it may hurt others in direct
5 and indirect ways. I, myself, would recommend -- I,
6 myself, would -- I think I'm supposed to say what I
7 think and I think that -- I would say that I would not
8 think that this is at this point ready for approval.

9 If the panel disagrees with me and it is
10 approved, I would have numerous comments about the
11 labeling that we see in the proposed commercial
12 materials. If I'm supposed to, I would be happy --
13 I've made some notes on that and I could comment here
14 or leave that for later.

15 DR. IBBOTT: I think we get to that later.

16 DR. STARK: Okay. Thank you. Thank you,
17 everybody.

18 DR. IBBOTT: Good. Thank you.

19 Dr. Blumenstein.

20 DR. BLUMENSTEIN: Amazing. It worked. I
21 wanted to say a few words about my thoughts on the
22 statistical concerns, some of which you've heard

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1 already a bit this morning.

2 First of all, I want to say that it
3 appears that the sponsors have done a really excellent
4 study according to today's standards. Nonetheless, I
5 can't escape concerns about the success and impact of
6 the device. These concerns are related simply to the
7 assessing the significance of it. Most of the
8 concerns that I have are rooted in the unique features
9 of the study design rather than the methodology that I
10 think has come to be accepted and used in this area.

11 In other words, there are unique features
12 of this study design that may make this difficult.
13 I'm not concerned about the general statistical
14 methodology and, in particular, the resampling part of
15 it, but I do have concerns about whether all the
16 important features of this study have been taken into
17 account in the resampling methodologies. Let me
18 explain that.

19 The first major class of discomfort I have
20 is the accuracy of the measures of success. In
21 particular, it's translation to the clinical measures
22 of success. In particular, we see no measures of

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1 uncertainty for the clinical measures.

2 In other words, the Az measure something
3 about device performance and not clinical performance.

4 While we have been given some indications of clinical
5 performance by showing ROC curves, little arrows, and
6 performance points and so forth, we don't have any
7 measures of uncertainty with respect to those clinical
8 measures.

9 I'm concerned about the sampling for the
10 cases that were included in this study. They were
11 artificially sampled. Population prevalence is likely
12 not reflected in the data set that was analyzed and,
13 therefore, it's difficult to assess a clinical impact
14 of these results without some kind of an assumed
15 prevalence. This is just sort of fundamental in any
16 kind of a diagnostic evaluation. I'm not sure this
17 could be avoided. I'm not sure how to deal with it
18 but it does leave me with some concerns.

19 Perhaps one of my major concerns is this,
20 that there is a correlation structure having to do
21 with this quadrant implementation which was some kind
22 of a partial localization methodology. I'm concerned

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1 that the correlation -- well, add a parentheses here.

2 That the correlation between the upper and
3 lower quadrants on the right lung, that is the results
4 from these quadrants, is likely to be larger than the
5 correlation between, say, the upper right and the
6 upper left quadrants in the same patient. In other
7 words, there's more correlation within a lung than
8 there is between quadrants of opposite lung.

9 I didn't see the computations took this
10 into account in any explicit way. I'm not sure how
11 you would. I'm just expressing a concern here.
12 There's a lack of complete understanding of the
13 methods used to analyze this kind of a partial
14 localization maneuver to get to these quadrants.

15 I'm also concerned about whether the
16 panel, the expert panel, had knowledge of the
17 patient's identity -- I assume that they did. I don't
18 see any evidence otherwise -- so that when they were
19 making a judgment as to the status of the quadrants
20 within a patient, that the results of one quadrant may
21 have left them to feel differently about the results
22 in the other quadrants as they were looking at these

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1 things. I don't see that taken into account. I'm not
2 sure how to do it and so on. I'm just concerned about
3 it.

4 Then I'm concerned about the incremental
5 structure of the study. The instructions to the
6 readers were definitely additive. In other words,
7 they were supposed to use traditional methods and then
8 add the CAD. The computations apparently didn't take
9 into account the correlation between methods. That
10 is, this is a correlation between methods, not the
11 correlation between quadrants of the lung and I didn't
12 see that.

13 I'm not sure this makes a difference but
14 I'm left with a feeling that it should make a
15 difference and it should have been taken into account
16 because the computational methods of ROC curves and
17 comparing areas of ROC curves and so forth seem to be
18 based on having done independent assessments of the
19 two methods. Therefore, I'm left to wondering whether
20 the p-value would be different had the correlation
21 between methods been taken into account.

22 And, finally, in this area of concern is

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1 the intra-reader variability. The experiment didn't
2 measure intra-reader variability by giving a given
3 reader multiple opportunities to read an image from
4 the same patient and, therefore, you don't know how
5 that read is going to perform. How much variability
6 there is going to be from seeing that same patient
7 over and over and you would want to do that in a way
8 that they wouldn't know it was the same patient if you
9 separated in time and so forth.

10 But how much would a measure of intra-
11 reader variability modify the p-value associated with
12 Az? I don't know. I was trying to get at that this
13 morning and apparently there's not much understanding
14 of that yet. But my intuition is that the intra-
15 reader variability would be particularly important in
16 the computations of variability for clinical measures.

17 It kind of goes like this, that the artificial
18 scaling of measuring on a probability scale, or
19 however you do it, in order to be able to use ROC
20 methodology depends on assumptions about the
21 performance of the reader with respect to their
22 consistency over use. Yet, the clinical measures that

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1 depend on that ROC don't take that into account so I'm
2 left with a bunch of concerns about whether had intra-
3 reader variability been taken into account whether we
4 might be seeing different results.

5 Then I have just another concern or two,
6 this business about truth. I think it's important to
7 note that the statistical methods absolutely depend on
8 a definition of truth, but I feel that the sponsor did
9 the best that can be done. I have no criticism of
10 that.

11 But it's important to realize that the
12 results are conditional acceptance of the definition
13 of truth as they got from this panel. Then what was
14 going on was that they degenerated truth and I found
15 that really weird. I couldn't think of a better word
16 for it. Sorry. I wondered why the impact on the
17 variations in readings couldn't have been done.

18 For example, I would have liked to have
19 seen some co-variate analyses or some sampling of
20 quadrants or sides of the lung. I don't know how to
21 do these. I'm just throwing these up. I hope some
22 statistic students are listening. Maybe it's an area

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1 of methodologic research.

2 The readers are using readers with smaller
3 or larger areas. This could be like a co-variant or
4 readers with more or less experience. Or what I think
5 is particularly promising is maybe you perturb some of
6 the thresholds that individual readers are doing and
7 this might be some kind of a Bayesian analysis whereby
8 you throw in some kind of a distribution of thresholds
9 getting back at that intra-reader variability.

10 At any rate, I'm of mixed mind. I'm
11 trying to be here but I think I'm here. Where I can
12 read that, it says, "I am a bomb technician. If you
13 see me running, try to keep up."

14 DR. IBBOTT: Thank you, Dr. Blumenstein.

15 All right. At this point we will see the
16 questions that the FDA is going to ask of the panel.
17 We will take a break shortly after that. When we come
18 back we'll consider those questions. I believe Dr.
19 Sacks is going to project those questions. When we
20 come back from our break, the first thing we will do
21 is address the questions to the sponsor and hear your
22 responses.

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1 DR. SACKS: Okay. I'll go through these
2 slowly but I think you have printed copies of them.
3 This is more for the audience.

4 First, please discuss whether the data in
5 the PMA support the conclusion that the CAD can reduce
6 observational errors by helping to identify overlooked
7 actionable lung nodules on chest CTs. In particular,
8 given that use of the CAD produced a statistically
9 significant improvement in ROC performance, please
10 discuss whether:

11 (A) The use of an expert panel is
12 appropriate for determining actionable nodules given
13 that a tissue gold standard is not feasible.

14 (B) Actionable nodules are a reasonable
15 target for a lung CT CAD to be judged safe and
16 effective.

17 (C) The achieved gain in ROC performance
18 in terms of the area under the curve demonstrates
19 safety and effectiveness of the CAD.

20 Second, please discuss whether the
21 labeling of this device including the indications for
22 use is appropriate based on the data provided in the

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1 PMA.

2 Third, please discuss whether the sponsors
3 proposed training plan for radiologists is adequate.
4 If not, what other training would you recommend?

5 Four, if the PMA were to be approved,
6 please discuss whether the above or any other issues
7 not fully addressed in the PMA, (A) require post-
8 market surveillance measures in addition to the
9 customary medical device reporting, etc., and (B)
10 suggest a need for a post-approval study.

11 DR. IBBOTT: Thank you, Dr. Sacks.

12 All right. We will take a 15-minute break
13 and we'll reconvene at 10 minutes to 3:00. Thank you.

14 (Whereupon, at 2:36 p.m. off the record
15 until 2:55 p.m.)

16 DR. IBBOTT: Thank you. We'll continue
17 now with the discussion and we are going to go
18 straight to a response from the sponsor to the
19 questions that were raised before lunch. I believe
20 Dr. MacMahon is going to start with that response.

21 MR. MacMAHON: Thank you. Again, I'm
22 Heber MacMahon from the University of Chicago. I

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1 would just like to start out by making a few points
2 that may clarify some of the issues that have been
3 raised. Let me start by just mentioning a few smaller
4 issues that have received a lot of attention.

5 Briefly, the question of the placebo
6 effect. Dr. Stark has raised the question whether the
7 need for the observer to review the case a second time
8 after being prompted by the CAD may have actually
9 improved performance because anytime there's a second
10 read, there's reason to believe that additional
11 nodules may be noticed.

12 However, I think it's worth emphasizing
13 that the average false positive rate of this system is
14 three per entire examination. We're talking about
15 examinations with up to several hundred sections.
16 What the observer does in those situations is not re-
17 read the entire study but go directly to those
18 sections on which he or she is prompted an average of
19 three sections and just look at that particular mark
20 and decide is that a nodule or not.

21 I would suggest that the opportunity for
22 picking up additional true positives in that situation

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1 is really pretty small if one looks at the number of
2 sections and the number of false positives with this
3 system. I would just like to make that comment.

4 But the larger issue I would like to talk
5 about, and I think it touches on all of the questions
6 that have been raised, is why is the difference in Az
7 so small in this experiment? I think there is a sense
8 of disappointment with what looks like a very strong
9 CAD detection system. We didn't see a larger
10 improvement.

11 I would suggest if we had a larger
12 improvement that a lot of the questions about the
13 statistical methodology and the design of the
14 experiment would become moot because it would become
15 apparent that such a large improvement could not be
16 accounted for by some of these issues.

17 We have had a discussion, and both Dr.
18 Wagner and Dr. Stark mentioned, in observer
19 performance tests it's not like real life. I can
20 attest to this. I've conducted several observer
21 performance tests myself, mostly related to digital
22 chest radiography and image processing. I have to say

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1 if I had conducted my experiments in this way, I don't
2 think I would have achieved even statistical
3 significance in most cases and I probably would be
4 here now.

5 Let me explain why. There are a number of
6 factors going on in an observer test. We've already
7 heard how the observers are working in an undisturbed
8 environment. They are highly motivated. They are
9 highly vigilant. These are radiologist.

10 We are sitting them down and we are
11 saying, "All you have to do is find nodules. We are
12 going to measure your performance and see how good you
13 are. You don't have to look at the mediastinum. You
14 don't have to look at the pleurae.

15 You don't have to consider interstitial
16 lung disease. We are not going to disturb you. The
17 telephone is not going to go off. The technologist
18 isn't going to tell you there is a patient on the
19 table for a biopsy. A clinician will not stop by and
20 ask you to look for a study." This is an ideal
21 reading environment.

22 For these and many reasons, the

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1 performance in an observer test is extremely high.
2 Basically observers do not miss obvious abnormalities
3 by in large in an observer test. But we know from our
4 own experience and from studies that have been done
5 that radiologists miss relatively obvious
6 abnormalities all the time every day.

7 That is actually the issue we are trying
8 to address and that is the difficulty in trying to
9 extrapolate from an observer test to clinical
10 practice. I would put it to you that these observers
11 were working on an extremely high level. If we look
12 at the average Az before CAD, the average was 0.88.
13 Some of the observers were over .9.

14 In my experience when you start at this
15 level in your unaided situation whether it's some kind
16 of image processing or energy subtraction or whatever,
17 it is very difficult to show a substantial
18 improvement. There is not a lot of room left for
19 improvement when the observers are right up there.
20 The situation we do see a large improvement is when
21 they start out at a lower level missing a lot of
22 abnormalities that then they can pick up in the second

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1 reader situation.

2 So what happened here and why did they
3 perform so well? Not only the observer situation but
4 the selection of the cases. In many observer tests
5 and the ones that we quoted in the literature that
6 show a large difference, we tend to go to difficult
7 cases because we know it's only in those difficult
8 cases that our CAD or whatever will make a difference
9 so we go to selected cases, perhaps cases that were
10 missed on the original reading, or perhaps a panel go
11 through and selects chest radiographs that have subtle
12 nodules.

13 This is a very well accepted way of doing
14 it because we know in those kinds of cases whatever is
15 the modality is likely to make an impact. Although
16 these are selected cases, we know it is usually
17 impractical to take a random selection of the whole
18 population and expect that there will be enough of
19 those subtle cases for the difference to be
20 statistically significant. We do some kind of
21 selection in most cases.

22 However, here although the cases were

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1 selected for having a high probability of nodules, and
2 there was a high incidence of nodules there, they were
3 not selected for having subtle abnormalities. We have
4 to assume that most of the nodules were easy. Most of
5 the observers detected them and, therefore, there was
6 no opportunity for the CAD to show an improvement.

7 So I think that this is a critical point
8 and to me this explains why that apparent improvement
9 is small in the observer test. I strongly believe
10 that if this kind of a system were implemented in
11 clinical practice where we were subject to these
12 various distractions where obvious abnormalities are
13 missed, there would be a much larger improvement and
14 this would be a useful clinical system.

15 In that regard, even if the amount of
16 improvement shown in the observer test were going to
17 be the amount of improvement in clinical practice, I
18 would say in my own practice where I encounter a high
19 proportion of patients with pulmonary nodules,
20 certainly larger than 1 in 100, I don't know exactly
21 what the number is but I would say up to half of all
22 the CT scans that I read have either a nodule or a

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1 question of a pulmonary nodule.

2 This is a very pervasive issue that
3 affects almost every CT scan we read. In some
4 screening studies the incidence of nodules has been
5 over 20 percent. Indeed, the incidence of even cancer
6 in some screening studies has been up to 2.7 percent
7 in the initial prevalence screen so nodules are not
8 rare abnormalities.

9 If I can reduce my missed rate by 15
10 percent or anything in that area, I would be very
11 happy because that is going to benefit a lot of my
12 patients. I'm going to see a benefit multiple times,
13 probably at least once a day. I would say throughout
14 the whole country the magnitude of that improvement is
15 not at all meager or insubstantial.

16 On that point I would like to hand off to
17 Dr. Castellino who has some more comments.

18 DR. CASTELLINO: I just have a few. I
19 think Dr. MacMahon has addressed some of the issues
20 that I was going to talk about but he certainly can do
21 it better and with more authority.

22 I would like to clear up the issue by

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1 consecutive cases. These were consecutive cases.
2 They were not selected for nodules. It turned out
3 that the practice where we got them from had
4 distribution of cases by report with nodule and cases
5 by report without nodules so there was no selection
6 whatsoever.

7 I would agree that I guess it depends on
8 your practice but if you're in a standard community
9 hospital or hospital setting of some nature, the
10 number of nodules you see on routinely performed CT
11 scans every day on a variety of patients, many of
12 which, by the way, happen to be oncology patients,
13 out-patient or in-patient, is high.

14 There was a comment made something like,
15 "We don't want to have the radiologist work for CAD."

16 I agree. We don't want to have the radiologist work
17 for CAD. In fact, I don't think the radiologists do
18 work for CAD if the nature of our product is correctly
19 understood.

20 The only additional work that is required
21 by the radiologist is to go back and review those
22 several slices, two, three, four, five, whatever it

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1 might be, look at the circle on the image and
2 determine if it's a true positive or false positive
3 study.

4 Now, we have not quantified how long
5 additional time that would take but it probably takes
6 in the order of anywhere from -- if there are no
7 marks, of course, it would take no seconds to maybe 15
8 or 20 seconds. There may be a nodule that is pointed
9 out that the radiologist has to think about and make a
10 clinical decision.

11 That often takes time but that's perfectly
12 fine. That's the whole point of the product is to get
13 the radiologist's attention directed at something that
14 may be important and then to tease it out and decide
15 what has to be done.

16 I would echo the fact that a 20 percent or
17 30 percent reduction in nodules that are missed might
18 represent only a five percent increase in the nodules
19 that I detect. I personally think that is a very
20 substantial improvement in my performance. That is a
21 very important issue.

22 I think that I would like to say that

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1 perhaps when residents of radiology finish four years
2 of training and they go on to a year of fellowship.
3 If we can improve their performance and their
4 subspecialty by five or seven percent compared to the
5 general radiologies of training, that is probably a
6 significant improvement. I don't denigrate the number
7 whatsoever. In fact, I think it's an important number
8 in clinical practice.

9 There was a comment about the radiologists
10 may not follow the rules. I think it's an important
11 comment. We don't expect that to be the case.
12 Certainly when we introduce a breast CAD product, as
13 far as we could tell they were following the rules
14 pretty assiduously.

15 Certainly for the masses which the code is
16 not anywhere nearly as perfect as it could be or as
17 robust as it could be. But I think that is probably
18 true of any device you have to consider. Often if
19 there are physicians out there that will use device
20 incorrectly, I don't know how you address that but
21 certainly that is not the point of how our device is
22 supposed to be used.

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1 Lastly, I think it's important to note
2 that should we gain approval and if there are post-
3 market follow-up studies that are recommended, that
4 should be done to further investigate the performance
5 in the real world. We obviously would discuss this
6 with the FDA and would be very happy to do that.
7 Thank you.

8 DR. IBBOTT: Very good. Thank you.

9 We are now going to consider the questions
10 and also the panel's questions regarding the
11 presentation. What I would like to do given the time
12 is ask that the first question be projected again. I
13 would like to ask the panel to consider the questions
14 one at a time -- we have the four questions and these
15 have been distributed to us -- and use this as our
16 opportunity to ask further questions of the sponsor as
17 they are relevant to the questions that we've been
18 asked to consider by the FDA.

19 While Dr. Phillips is getting that up,
20 I'll remind you the first question is to discuss
21 whether the data in the PMA support the conclusion
22 that the CAD can reduce observational errors by

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1 helping to identify overlooked actionable lung nodules
2 on chest CTs.

3 In particular, given that the use of the
4 CAD produced a statistically significant improvement
5 in ROC performance, please discuss whether (A) the use
6 of an expert panel is appropriate for determining
7 actionable nodules given that a tissue gold standard
8 is not feasible.

9 I would like to invite the panel now to
10 discuss this question. I throw it open to anyone who
11 would like to lead off.

12 DR. KRUPINSKI: Offhand I would say yes,
13 it is. I mean, I don't see really that many other
14 ways to do it and I think the analysis where they
15 broke down and showed the different ways of doing it,
16 leave one of the observers out, put them back in. I
17 honestly don't think there is any other way at this
18 point in time that you could get at some other truth
19 than using an expert panel. I think it was
20 appropriate.

21 DR. IBBOTT: I would be interested in
22 knowing from the radiologists on the panel and other

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1 people in the room if the variability among the panel
2 that developed the reference standard if that sort of
3 variability seems to you to be typical. I know
4 radiologists don't agree with each other 100 percent
5 of the time. I'm not naive but I do want to know if
6 the sort of differences that we're seeing here if you
7 believe those are representative.

8 DR. CONANT: On a good day or a bad day?
9 I think definitely. I think they did a very eloquent
10 job of creating the expert panel and coming up with
11 really the best situation possible in this case.

12 DR. TRIPURANENI: I echo the same
13 comments. As a clinician that is the vagaries of the
14 clinical practice and I think what they defined as
15 actionable module I think is probably the best that we
16 can do today.

17 DR. IBBOTT: There seems to be agreement
18 then.

19 DR. STARK: One question along those
20 lines, Mr. Chairman, is that making the most
21 benevolent presumption, I mean, that on its face it
22 looks like they've done absolutely everything that

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1 could be done but this is a very, very complicated
2 business of selecting images. All sorts of selection
3 biases, even selecting in the institution and the CAT
4 scanners. There can always be more information on
5 this that I think the FDA should consider.

6 We have an able group of FDA staffers and
7 so I think how these patients were selected, the
8 institutions that were selected, why not more scans
9 from certain institutions that are clearly generating
10 them if these were consecutively obtained.

11 I think for any further studies whether
12 they are done for a PMA revision or post-market
13 surveillance, I think more information on why this
14 number of exams from these institutions. I think it
15 should be offered because it will lead to more
16 questions which if nothing else will advance the
17 science that has already become quite sophisticated
18 here.

19 The other thing is that I do believe that
20 we should learn whether the truth in this case that we
21 are all saying was reasonable when these cases were
22 gathered two years ago, did it work out that way

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1 because we know more, or the industry, the applicant
2 knows more about these patients today. I'm very keen
3 to know these people with nodules have had follow-up.

4 These actionable nodules we have proof on.

5 I don't know if I missed it but I would be
6 keen to know how many of these were reasonably deemed
7 actionable but turned out to be benign and did not
8 change and did not require treatment and how many that
9 were considered not actionable turned out to be
10 cancer.

11 That's not only important for this product
12 but for its post-market surveillance and the
13 development of new algorithms for improved products in
14 the future.

15 DR. IBBOTT: Are you asking the sponsor
16 that question?

17 DR. STARK: If I'm permitted. I really
18 would like to know what using a different -- using the
19 real world clinical definition how many of the
20 actionable nodules were actionable and vice versa.

21 DR. IBBOTT: Yes, Dr. O'Shaughnessy.

22 DR. O'SHAUGHNESSY: Yeah, I think that's a

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1 very good point. Basically we designed protocol in
2 consultation with FDA. We identified who the people
3 were that would qualify for including in the study.
4 Because of both IRB and other issues, the sponsor is
5 blinded to who the patients are and the follow-up, we
6 collected a prespecified certain amount of
7 information.

8 If necessary, we can't work with FDA to
9 determine if it's possible and if we could go forward
10 to find out what happened with these patients. Again,
11 they were collected with a certain concept in mind to
12 do the study.

13 DR. STARK: Thank you.

14 DR. IBBOTT: All right. Are we ready to
15 go on to the next question? Okay. The next question
16 asks us whether actionable nodules are a reasonable
17 target for a lung CT CAD to be judged safe and
18 effective.

19 DR. KRUPINSKI: Again, I would say it's
20 reasonable given the caveat that Dr. Stark brought up.

21 If you could follow up on these and find out if they
22 truly were actionable versus not, that would certainly

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1 be a benefit. I think that is the most reasonable
2 thing for it to be looking at.

3 DR. IBBOTT: Yes, Prabhakar.

4 DR. TRIPURANENI: It's interesting. It
5 all depends on how you define safety and efficacy. I
6 think Dr. Stark called it on this one. As a
7 clinician, to me the effectiveness is ultimately
8 consulate to whether it has any clinical impact. To
9 me, it's really up to the management of the patient
10 and ultimately what he's going to do.

11 I really can't answer this question at
12 this point in time because I just don't have enough
13 information to say that it is actually effective at
14 this point in time. Yes, the statistics and you
15 picked up a few extra nodules but I really would like
16 to see the clinical data. I do understand that's not
17 how the protocol was designed but I strongly recommend
18 that we really need to look at the information, what
19 is the ultimate clinical impact and the clinical
20 significance.

21 As far as the safety is concerned, I think
22 Dr. Bill Sacks already raised this question. I think

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1 it keeps bothering me that even though once the
2 product is approved, if the product is approved, when
3 it goes into the real world, it's quite possible that
4 there may be somebody might actually get a little
5 slack and actually not use the proper methodology that
6 was recommended. That is, read the whole CT scan
7 unaided before followed by using the CAD system there.

8 If the system is used as it is actually describe, I
9 think it is actually safe.

10 But, on the other hand, I keep thinking
11 whether there is a way you can actually come back and
12 make sure that the people do it the way they are
13 supposed to do but I can't think of any other way. I
14 don't have an answer. I'm just raising the question.

15 If somebody is not going to use the system as it is
16 supposed to use it, could it be potentially unsafe? I
17 don't know the answer.

18 I actually have a question for the
19 sponsor. In your 90 patients, 43 patients had
20 nodules. Were there any instances where the
21 radiologist unaided picked up the nodule but the CAD
22 missed the nodule completely?

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1 DR. CASTELLINO: I don't have the number
2 for that but the answer is, of course, it did. The
3 CAD system is not 100 percent sensitive unfortunately.
4 In fact, it doesn't mark a certain set of nodules
5 that the radiologist clearly sees. That's why it is
6 really viewed as an adjunctive review.

7 To sort of get at the prior comment, which
8 I think is a very good one, let me remind everybody
9 how the radiologist looks at the CT scan of the chest.

10 We give it at least two passes of the entire image,
11 maybe three. One is what we call mediastinal or soft
12 tissue windows looking for abnormalities in the
13 mediastinal chest wall, etc.

14 One perhaps is bone windows. Sometimes
15 is, sometimes not. And one is at lung windows. At
16 the lung windows we can see abnormalities within lung
17 parenchyma. Now, as we look through those 100, 250
18 images in a melt-through fashion, cine fashion, I
19 don't know of any radiologists who looks through the
20 entire data set saying, "I'm looking for nodules.

21 I'm looking for airspace disease. I'm
22 looking for bronchial wall abnormalities. I'm looking

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1 for emphysema." I'm looking for this, looking for
2 this, and looking for this. But instead we looked at
3 the lung images globally and we see if there are any
4 features within the lung parenchyma that shouldn't be
5 there.

6 Nodules, infiltrates, pulmonary
7 infarction, etc., etc. Just that alone means that the
8 radiologist has to look at every lung image either
9 individually or sequentially in some sort of more
10 efficient mode. No. 1 is that that's how it has to be
11 used. In the process a radiologist will detect
12 nodules.

13 Secondly, the radiologist knows that it's
14 not going to detect all nodules. If it ever got to
15 the point of 100 percent sensitivity, they could use
16 it only the first time as the first reader. We are a
17 long ways away from that. But they still would have
18 to look at all of the lung images to see everything
19 else. I hope I have answered that question.

20 DR. TRIPURANENI: I guess as humans we are
21 good at pattern recognition. That's what I do. Even
22 though I'm a radiologist and oncologist I keep looking

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1 at the CTs and all those things and we are good at
2 recognizing patterns. I guess the computer is not
3 quite dead yet.

4 I have another question which is the flip
5 side of the other one. How many patients did the
6 radiologist actually say there are no nodules unaided?

7 What percent of those patients did the computer
8 actually say there is a real nodule, that the CAD
9 really helped them to turn the negative nodule patient
10 into a positive nodule patient?

11 MR. MILLER: I think I'm probably the one
12 with your answer but I didn't quite get it. Would you
13 mind repeating? I think you're looking for a fraction
14 but what's the numerator and what's the denominator?

15 DR. TRIPURANENI: What I'm looking for is
16 if the radiologist read the scan and he basically said
17 there are no nodules in any of the four quadrants.

18 MR. MILLER: Yes.

19 DR. TRIPURANENI: And when you use the CAD
20 what percentage of those patients were turned into
21 positive nodule patients?

22 MR. MILLER: Right. That's this issue of

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1 the percent reduction in misses, I think. In order to
2 answer the question, you have to make assumptions
3 about what an individual reader's true threshold would
4 be. We really can't do that. We can speculate at
5 what the number would be if everybody's true threshold
6 was 20.

7 If everybody's true threshold was 20, then
8 they missed things on the first read 16 percent of the
9 time, then on the second read only 11 percent of the
10 time and that's a 30 percent reduction. If their
11 missed threshold was 80, then it's a different number
12 that I don't have at my fingertips. Is that answering
13 your question?

14 DR. TRIPURANENI: Partly. The absolute
15 number that you picked up was about 4 to 5 percent. I
16 think the improvement whether it is 20 or 80 percent
17 threshold is approximately 16 to 28 percent or
18 something like that.

19 I'm actually going back to the actual
20 number of patients right there. If somebody has three
21 nodules in one lung, it doesn't matter if you will
22 pick up two more nodules on that lung. What I'm

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1 really interested in is the patient who never had any
2 nodules in both lungs that the CAD helped to pick up
3 an extra nodule that would really make all the
4 difference in that particular patient.

5 MR. MILLER: I don't know the number on
6 that. I can tell you that there were a fair number of
7 patients like that. I mean, maybe about half of the
8 cases in our study only had a single nodule so for
9 that nodule to be identified caused the ratings to go
10 up. Again, I don't know the percentage but there were
11 quite a few cases like that.

12 DR. KRUPINSKI: Do you know the flip side
13 to that? How many of the absolutely normal patients
14 that the radiologist called normal and then the CAD
15 pointed something out and turned their totally true
16 negative into a false positive and now you've got a
17 false positive patient. How many of those?

18 MR. MILLER: I don't know that number.
19 Again, I know that there were patients like that but I
20 don't know the number. I would be speculating.

21 DR. SOLOMON: I think you're hearing the
22 question essentially of how do you translate the

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1 statistics into clinically significant issues. That
2 is, changing the patient who is negative into a
3 positive or whether it is significant if you add one
4 nodule and the sixth nodule.

5 MR. MILLER: I am hearing that and I think
6 that is something we can probably work with FDA on
7 from the data that we collected.

8 DR. CONANT: May I just say something
9 quickly in terms of answering this question? I think
10 actionable nodules are really the target that we have
11 clinically. It's wonderful to look for a two-year
12 follow-up or biopsy proof but that is not what the
13 task is at hand.

14 It's are we going to say short-term
15 follow-up. We need that stuff eventually and, yeah,
16 we're all curious about it but in terms of the
17 detection task, it's really an actionable nodule. I
18 agree that this is a good target but, again, I'm
19 concerned about looking at the data by patient, not
20 just by nodule or quadrant because it does make a
21 difference in patient management whether it's nine or
22 10 nodules versus zero to one so I agree and disagree

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1 with that.

2 The other thing I just really quickly need
3 to comment on is this comparison, I hate to do it,
4 with mammography. But, you know, I see CAD in place
5 of mammography and, yeah, people cheat. That's not
6 what this is about. This is about marketing and
7 education and you can't prevent people from cheating.

8 That's not really our task here. It does
9 happen but hopefully, you know, people will be better
10 at that. The thing about a chest CT is that this is
11 one task in that chest CT that they are being asked
12 and that this company is addressing so that this idea
13 of cheating, "I'm going to look at the whole CT but
14 I'm not going to look at nodules until I have my
15 prompt." I don't think we as a panel can really go
16 there but I've seen it happen. I don't do it.

17 DR. BLUMENSTEIN: How do you cheat?

18 DR. CONANT: I actually have not used --

19 DR. BLUMENSTEIN: It just doesn't seem --

20 DR. CONANT: I have to admit I have not
21 used CAD in clinical practice. I am waiting for it to
22 come off the direct digital images in my clinic. It

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1 used to be you digitize the images, you had your film
2 screen there, and you pushed a button and your little
3 prompt came up and you didn't have to wait until after
4 you saw the images.

5 You just pushed the button and you never
6 had to look at the images. Your answer was there.
7 Now, one think that has, or I think potentially could
8 be built into a soft-copy review of digital
9 mammography and chest CTs is a lag time before the
10 information is available, or the requirement to go
11 through the image with multiple window levels and
12 mediastinal and all that other stuff that chest people
13 do.

14 Potentially in mammography to prevent
15 cheaters you could say, "Okay, you've got to scroll
16 through every image on all the resolutions and stuff
17 before your CAD prompts will come up." Again, that's
18 not what we're being asked to create a safeguard
19 against cheating here, I don't think.

20 DR. SOLOMON: It's important for safety
21 issues and maybe even a warning that you had to click
22 before you actually -- you know, just a reminder to

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1 the average user that this is something that could be
2 dangerous unless you looked at the scan already.

3 DR. CONANT: But that's education and
4 training and eventually you're liable anyway.

5 DR. FERGUSON: My question is tangential
6 to this because as I listen to you describe the
7 instrument and its use, you said that -- I thought I
8 heard you say that the radiologist had to go through
9 the scan before he could click on your button.

10 I mean, is there a fail safe there which
11 keeps the radiologist in -- little or none of these
12 people are around, you understand, but where he could
13 go in and click and get your imaging for the whole
14 lung scan for nodules and then use those as his
15 reference points?

16 DR. IBBOTT: Actually, Dr. O'Shaughnessy,
17 I was going to invite you to come up and your
18 colleagues to come up to this table so you don't have
19 to keep jumping up and down. If you pull up a couple
20 more chairs, perhaps three or four of you could sit at
21 that table.

22 DR. O'SHAUGHNESSY: Thank you.

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1 DR. CASTELLINO: I perhaps was misleading
2 when I made that comment or wasn't understood. First
3 of all, let me emphasize there is no fail safe
4 mechanism. We thought about building that in in some
5 fashion. We feel that labeling and training will
6 address it. There are work-arounds if you made
7 everybody look at the lung windows first.

8 You go through the whole lung windows and
9 push the button so, I mean, we are very -- radiologist
10 are very clever people but I don't think it would
11 work. What I was trying to get across -- I see you
12 would agree with me.

13 What I'm trying to get across in looking
14 at, you have to look at all the lung windows for a
15 whole host of other abnormalities that are within the
16 lung of which nodules are one feature, let's say, of
17 maybe eight or 10 features that you're looking for.
18 Even if you push the button first and said there's a
19 nodule or two, you still are required to look at
20 everything because you have to do that.

21 I think radiologist will use it -- will be
22 more likely to use it in the prescribed fashion. With

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1 mammography it's different with the CAL code being
2 about 98 percent accurate, it's almost approaching 100
3 percent, yes, I think some radiologists probably do
4 use it as a first reader for CAL but certainly not for
5 masses.

6 DR. IBBOTT: Thank you. It, again,
7 appears that we have consensus on this second
8 question, that actionable nodules are an appropriate
9 target for this question.

10 So then the third question is the achieved
11 gain in ROC performance demonstrates safety and
12 effectiveness of the CAD. We've already been
13 discussing this to some extent. Clearly it does seem
14 to depend on how rigorously the radiologist followed
15 the always and the never rules.

16 Being people I'm sure that not everybody
17 will always follow the always and never rules. The
18 question is has the company done the appropriate
19 things to encourage people to use this device
20 correctly?

21 We've seen some of the information that
22 they have provided us today and there is a fair amount

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1 more in the information we've reviewed with the
2 labeling that describes the warnings. I would like to
3 ask how you feel if you haven't already volunteered
4 your opinions about the labeling and the adequacy of
5 these warnings if you consider that they are
6 acceptable.

7 I don't mean to swing us away if you view
8 that question as asking something a little different,
9 but certainly I think that the safety question is at
10 least partly dependent on people following the never
11 rule, not changing their diagnosis based on the
12 response of the CAD system.

13 DR. CONANT: Just real quickly, I'm very
14 positive about the first two. This one I have
15 problems with, though, because I don't think that
16 we've really definitely showed the effectiveness
17 without looking at this by case. You're actually
18 specifically asking her about ROC performance as the
19 measure of effectiveness. Until I have it broken out
20 by patient, I'm not really sure of that.

21 DR. BLUMENSTEIN: I see there's two
22 measures we have. We have ROC performance which, I

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1 think, is a measure of device performance. Then what
2 we've been talking around and we all seem to have some
3 degree of discomfort with is whether it performs
4 clinically the way that we would expect it to or would
5 hope that it would.

6 I have misgivings about whether the ROC
7 performance measures are accurate and I have expressed
8 those but I definitely have issues about whether
9 there's clinical safety and effectiveness demonstrated
10 because we don't have measures of confidence bounds on
11 sensitivity or any other kind of measure that shows us
12 an estimate of the clinical efficacy.

13 Now, I don't know whether the FDA is
14 inclined to give a device approval based on device
15 performance or whether there is a need for
16 demonstration of clinical effectiveness. But as a
17 panel member given the data that I have, I have to say
18 that the answer to C is no for me.

19 DR. SOLOMON: I have two questions for you
20 that are related to this. The first is that we
21 weren't presented with any data on reproducibility of
22 the system. I don't know if you have anything to say

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1 about that. If I ran an R2 on the same scan or same
2 patient, is it going to always give the same result?

3 DR. O'SHAUGHNESSY: In this particular
4 case -- this is Kathy O'Shaughnessy -- the images are
5 digital images so the algorithm will perform exactly
6 the same on the same digital image. Reproducibility
7 isn't an issue.

8 DR. SOLOMON: Okay. And then the second
9 question has to do with the fact that I guess you are
10 currently selling the product in Europe and I'm not
11 sure how many months now it's been that way but do you
12 have any feedback from the physicians in Europe who
13 are using the system? How is it working as far as
14 safety and efficacy goes?

15 DR. O'SHAUGHNESSY: It hasn't been on the
16 market very long in Europe so we only have a limited
17 number of sites. In terms of safety there's been no
18 adverse events certainly that have occurred with the
19 device. I believe that physicians are very happy with
20 the use of the system. They are not collecting
21 clinical data, as far as I know, that could be
22 supporting this application.

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1 DR. SOLOMON: Do you have any post-market
2 studies of data that you are collecting right now in
3 Europe?

4 DR. O'SHAUGHNESSY: No, we're not.

5 DR. IBBOTT: Yes.

6 DR. TRIPURANENI: Regarding the clinical
7 effectiveness, even though that is not the topic of
8 the discussion, we heard from Dr. MacMahon about what
9 he felt about this. I would like to ask, if the
10 Chairman lets me indulge, Dr. Delgado about his
11 particular clinical impressions.

12 I'm not talking about the protocol per se.
13 What is your feel having looked at 20 or 30 patients
14 in your institution? Do you think it's going to have
15 an impact on the clinical practice? Perhaps it's not
16 a fair question.

17 DR. DELGADO: Well, we did not do a
18 dedicated analytical study but we did get basically
19 comments from different radiologist of which I'm one
20 of them that worked with them. We do handle a large
21 volume of CTs per day and multi-slice CT cases.

22 Like I said, most radiologists found that

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1 there were nodules that we missed and increasing
2 nodule detection is something that I think is only a
3 good thing so I think it's effective in terms of what
4 it's stated to be, that is, increasing detection rate
5 of nodules. I felt that it's effective in what it's
6 stated to do.

7 DR. STARK: If I can touch on a couple of
8 things on this one seed. I mean, we see effectiveness
9 where the radiologists are limited so much in their
10 tasks and safe because they are constrained to just
11 looking at airspace without the distractions under
12 these conditions that we all agree are designed to ask
13 a very focused question designed for this ROC study.
14 But we don't know if the radiologists given whether --
15 I certainly agree with Dr. MacMahon's suggestion that
16 a more reasonable study group would have 80 out of 100
17 scans be completely normal and maybe 18 out of that
18 100 have some other abnormality like COPD, some
19 atelectasis or pneumonia or pleural effusion. And 2.7
20 out of that hundred should have perhaps solitary
21 pulmonary nodule because we can make arguments here
22 that you have perhaps undersold the technology that it

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1 might be particularly useful at helping the
2 radiologist find a needle in a haystack when he's
3 distracted, but it also has to show that is the
4 efficacy argument that has not been proved and it
5 might be better than what you say. It might be worse.

6 The safety argument is under those conditions can you
7 prevent these radiologists from falsely causing
8 additional scans, biopsies, etc., to fight off these
9 false positives when you do have to look at the
10 mediastinum and there is an infiltrate and there is
11 some adenopathy or some post-operative changes.
12 That's one issue in terms of the study population.

13 I also wanted to mention that I think my
14 colleague, Dr. Solomon's reproducibility question is
15 particularly important. What happens after a patient
16 has been operated on? We all agree that the computer
17 is going to run the same file the same way twice
18 absent, again, your flash card got overloaded with
19 photographs of mars. But what about the patient who
20 is scanned on another day and breathed differently or
21 had their arms by their side or had a contrast
22 injection? There must be data available to you that

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1 doesn't even require -- each patient serves as their
2 own control. I mean, just go into the archives at
3 Sloan-Kettering and you can come up with 100 scans
4 digitally, run them through your computers, and show
5 here are patients where we have six scans. We have
6 100 patients that have had six scans and how many of
7 those, if it's 20 percent have an abnormality, did
8 this machine treat that abnormality. That is a very
9 simple, not labor -- not even -- there's no physician
10 work at all. That would really answer the
11 reproducibility question in a clinical context and it
12 would show that doctors can rely on this from day to
13 day.

14 Lastly, I am concerned to hear that this
15 product has been in Europe. Clinical radiologists,
16 especially when something is this -- like surgeons
17 deciding lap cholecystectomy works. It's good for
18 patients. We decide based on word of mouth,
19 anecdotes, and I very much appreciate Dr. Delgado's
20 excellent presentation of his anecdotal experience.

21 It brings this to life but where are the
22 European papers saying, "This has changed my practice.

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1 This has made my life easier. I feel more
2 comfortable." There are usually anecdotal reports at
3 levels that have a less of a standard than we have
4 here like the RSNA or national meetings and why aren't
5 they appended as written testimonials at a higher
6 level than, forgive me but, you know, from one user at
7 a beta test site. Where are the published
8 testimonials or anecdotes or clinical case reports in
9 the literature of Europe?

10 DR. IBBOTT: Yes, please.

11 MR. MacMAHON: I think there were a number
12 of issues. One was a suggestion of doing the observer
13 test in a different way, perhaps with more normals and
14 with multiple kinds of abnormalities in the spin. I
15 agree that would be ideal in a sense.

16 I should point out there were multiple
17 abnormalities in the scans that were used. These were
18 not just pristine normals versus typical nodules. I
19 think, in fact, you saw in the really typical
20 classical nodules the results were much more
21 impressive.

22 A lot of the disagreement among the

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1 radiologists in nodule detection, I think, although I
2 didn't participate, was not so much is this a nodule
3 or a vessel. It was does this qualify according to
4 these very specific criteria as an actionable nodule
5 above a certain size and above a certain density, when
6 does it become a scar or when does it become an
7 airspace opacity.

8 Those are the things we struggle with
9 every day. That was partly a matter of definition.
10 But I think the mix of normals and abnormal was used
11 to maximize the statistical power in the experiment.
12 Of course, one could do more ideal experiments if time
13 and money are no object but this was already pretty
14 extensive. I think that was probably a reasonable
15 approach.

16 There are some other issues. Perhaps I'll
17 have the other people address them.

18 DR. CASTELLINO: Well, just a couple
19 comments. It turns out, it just so happens, that half
20 of the patients in the 90 group study, 45, were done
21 with bolus IV contrast injection and the other half
22 were not so we didn't design it that way. It just

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1 happened to fall out that way. We saw no difference
2 in the appearance of the nodules. In fact, with
3 contrast you may expect some of these things might be
4 easier to detect.

5 To answer one of the questions, I would
6 like to reemphasize we didn't cherrypick for clean
7 lungs. We had an independent radiologist come in and
8 rate the lungs as clean, intermediate, or dirty. I
9 don't know the exact numbers but I think something
10 like 15 percent would be dirty lungs, about 30 or 40
11 percent intermediate, and the other whatever remained
12 would be relatively pristine lungs. As I said before,
13 a number of these patients did have prior surgery or
14 radiation therapy. They were included in the study
15 group.

16 I would dearly like to go into Sloan-
17 Kettering's Radiology Department or any other
18 radiology department and get a bunch of cases like I
19 used to do and do clinical studies. I can tell you
20 trying to get cases from institutions to do this type
21 of research work is extraordinarily difficult. I know
22 the academic community is very aware of this. We are

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1 trying to develop both databases so everybody can have
2 access to it. Let me tell you, this is not a trivial
3 issue. To identify these five sites you've got the
4 cooperation from these people and it is extraordinary
5 and we are deeply indebted to them. I think your
6 suggestion is great. You get me the studies and we'll
7 do the research on it.

8 Reproducibility. I think the issue with
9 mammography, and I don't like to keep bringing this
10 up, but when you're scanning a film the noise within
11 the scanner, the digitizer, is a problem with
12 reproducibility. We've done those with film base
13 studies. With a digitally acquired image, there is no
14 issue for the algorithms since it has always worked on
15 the exactly same digital data set.

16 Going from one patient to the next, it all
17 depends on how that patient is. Two days later the
18 patient may have motion artifacts and what not. The
19 CAD obviously will perform different on that type of
20 case material.

21 Lastly, there are some reports that were
22 presented with this product. I'll be glad to get them

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1 together and ship them out to you guys to take a look
2 at. They are all, of course, retrospective studies
3 looking at cases where red is negative, reviewed in
4 retrospect to see were there nodules in the lung and
5 CAD identified a number of nodules.

6 One comes out of Brigham at Harvard.
7 Twenty-two percent of the cases were negative for lung
8 nodules, not other abnormalities. They found nodules
9 that they felt were important to recognize in
10 retrospect, 22 percent of the cases. Oh, I just
11 answered that question. Okay.

12 DR. IBBOTT: How about Nancy since you
13 haven't said anything.

14 MS. BROGDON: I just wanted to comment.
15 When you mentioned shipping some information out,
16 please make sure that anything that you submit comes
17 to the agency directly. Thank you.

18 DR. CASTELLINO: Absolutely.

19 DR. IBBOTT: Dr. Krupinski.

20 DR. KRUPINSKI: An issue sort of following
21 up on what was already brought up. Not reliability
22 but engendering trust in your users. I notice that

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1 when you're reporting the false positive rates on the
2 stand alone you report median. Now, typically median
3 is used when you have a skewed distribution so I'm
4 assuming that you are negatively skewed and your false
5 positive rate the average was higher than the median.

6 Could you tell me what the average was, was it
7 skewed, and then the range of false positives per
8 case. Not just the median because two to three median
9 most people are going to look at that and say average.

10 I think it might be a little bit misleading.

11 MR. MILLER: I agree. People use the word
12 average sometime to mean either a median or a mean and
13 I think we have to be very careful not to refer to
14 that number as an average because the distribution is
15 skewed and the median and the mean are different.

16 Because there are some patients that could
17 actually have 100 nodules, we don't have a cap on the
18 number of marks. The system could actually find 100
19 true positives on a given case so we actually do have
20 one case out of the 151 that had 47 false marks.

21 Now, I think on that case when people hit
22 it they sort of just ignored all the marks because it

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1 was just obviously a very, very dirty lung. I don't
2 know the number off the top of my head but I think the
3 mean false marks is four if we are defining false as
4 marks that were not panel findings at all.

5 If we include some of those equivocal
6 findings, the one-thirds and the two-thirds, I think
7 it may go up to five and the number is different if
8 it's false marks per normal case or total number of
9 false marks. That's in the ballpark of what it is.

10 There are actually a fair number of cases
11 with zero marks. A lot with zeros and ones and so
12 forth so that's where it goes back to your other
13 questions about correctly localizing.

14 DR. KRUPINSKI: This is unrelated but did
15 you look at the stand-alone performance was very
16 different from the ROC analysis? You broke this now
17 into classic versus nonclassic. Did you go back and
18 look at the performance data of the observers using
19 that breakdown instead of what was used?

20 MR. MILLER: Yes, we did, using a cut
21 point of the four-fifths classic so if you -- we don't
22 have the distribution here but it's sort of split out

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1 neatly that people are more likely to be on one end or
2 the other so using that four-fifths definition you
3 actually get more of a separation of the curves than
4 we do with what we showed you. I think that is
5 essentially that we have a higher true positive
6 percent and people are reacting more often to it.

7 DR. IBBOTT: Okay. I think then we'll go
8 on to the next question. Question No. 2 then is
9 please discuss whether the labeling of this device
10 including the indications for use is appropriate based
11 on the data provided in the PMA. This is, again, on
12 the question of are the instructions for use and
13 warnings about the always and never rule sufficient.
14 Maybe we have discussed that enough. I'll see if
15 there are any comments from the panel.

16 DR. STARK: I have a few. If people could
17 turn to Tab 8. I'm not sure if I've directed myself
18 to the most important place but this is where I've
19 taken off. I think, by the way, since I'm a primary
20 reviewer I should fill in some of these things.

21 Suffice it to say I would like to conclude
22 -- I conclude from the discussion that I've heard

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1 today that the word "significant," that if this
2 product is approved now or in the future, any claim to
3 significance really should be toned down.

4 I don't know -- I'm not trying to lawyer
5 anybody here. I know there are people in the FDA that
6 know how to do this but I would be offended to see the
7 word. I think there is a future for this technology.

8 I'm not sure today is going to be the biggest step
9 forward but it's definitely positive or negative
10 result in terms of approval.

11 This is a step forward because there is
12 going to be this technology but I do not think we are
13 close to where I would feel comfortable being part of
14 something where a radiologist is told that this
15 product makes a significant difference. I think this
16 is an aid like a better light bulb in a view box.

17 I mean, I think it should be -- if you are
18 allowed to sell this, I think the word significant
19 should be in a footnote and only when it's within two
20 words, if you put it in Google, of the word ROC so
21 that we have a significance statistical ROC result in
22 a footnote.

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1 But to tell radiologists this is going to
2 make a significant difference in their practice or
3 significantly help their patients, I think this panel
4 and everybody who has been candid have labored
5 mightily to say that is not a correct claim and it
6 would be misleading. I would rather be on the
7 plaintiff side of a malpractice suit related to that.

8 Similarly, for example, some of the
9 language that I would use as an example, and, again,
10 I'm not trained in this and forgive me for being
11 blunt. I'm just trying to help because I'm presuming
12 in these comments that there is something to be
13 decided here and we're just talking about language.

14 The phrase under efficient detection of
15 lung nodules, paragraph 2, second sentence. By the
16 way, here is an example of the confusion. You have
17 clinically significant nodules here and elsewhere the
18 word significant is used and we talk about it being
19 loaded, spun, twisted by our presumed innocence but
20 marketing people will get carried away and you would
21 be on the edge of fraud just due to concatenation. So
22 forget about that word significant, but high

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1 sensitivity and low false positive CAD marker rates, I
2 do not see how someone can make that concatenation.
3 That is just to me a little bit too artful.

4 We have a very high rate of false
5 positives with CAD. I mean, to characterize what we
6 are having as CAD marker rates as low false positive
7 is the exact opposite of the truth. Again, this is my
8 opinion. I would love to parse the language if that
9 is what we are supposed to do here.

10 Let's see. In terms of improving
11 sensitivity and efficiency, the sensitivity argument,
12 I think that may pass mustard with an asterisk. I
13 don't know that we've shown there is any increase in
14 efficiency at all. I really don't. I think we have
15 said basically to the radiologist read it again.

16 I would like to -- I appreciate the back
17 and forth and I think everything Dr. MacMahon said is
18 correct and everything that I have said is correct as
19 we, again, focus people on this. You are redirected
20 to a single slice and perhaps the computer work
21 station, whatever it cost, leads you to that slice but
22 no radiologist is going to decide real or not real

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1 based on looking at that one slice.

2 They are either going to tile up the
3 adjacent slices until they are fully through the
4 lesion, or they are going to trackball through it and
5 in most cases human nature you are going to trackball
6 through a significant fraction of the images.

7 All I can say is touche, back and forth on
8 this. You are not just going bing, bang, boom, there
9 are three slices it picked out. They were all
10 obviously nothing. No way. No way at all that's
11 going to happen. You are going to trackball through
12 it and that's going to take time. I think the
13 efficiency claims really would have to go.

14 On the next page where it says, "Automatic
15 CAD processing or lung nodule detection requires no
16 user interaction." Again, please, my opinion is that
17 I know some person probably was just being
18 enthusiastic but this requires that the radiologist be
19 responsible for dealing with this snow storm of false
20 positive exams.

21 It's the worse kind of user interaction.
22 It's the kind of user action that causes radiologists

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1 to stop doing mammography or to leave the field
2 entirely. It's like I'm going to say there's all
3 these positives here and I'm going to be a malpractice
4 lawyer's dream. Now you have to bat away all of these
5 snowflakes and take the time to interact.

6 Definitely have to interact and take the
7 time to do it and be liable. I doubt this is
8 something that should be considered here but the
9 affect on people's ability to read, the psychodynamics
10 that produces these ROC curves, that produces
11 radiologist's performance really is largely affected
12 by people's anxiety and I know there are people here
13 that are expert on that and I'm not.

14 But I think it's going to make people very
15 edgy and it's going to have a lot of unintended
16 consequences that they are going to be thinking about
17 what's the malpractice lawyer going to do with or
18 without application of this approved technology.

19 That alone might have a bigger affect on
20 reader performance. Those of us who don't have the
21 machine will be more careful and those that do may or
22 may not be more careful. I think the labeling and the

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1 training is extremely important. I know we'll get
2 into the training next.

3 DR. CONANT: May I say something real
4 quickly?

5 DR. IBBOTT: Yes.

6 DR. CONANT: Just a little rebuttal there,
7 Dr. Stark.

8 DR. STARK: Please.

9 DR. CONANT: Sorry, David. From
10 experience in breast imaging, I just have to say two
11 marks is not a high false positive rate. When I'm
12 looking at the task at hand which is 300 images, I
13 don't know that's a high false positive rate until I
14 know how it impacts a single patient.

15 It doesn't sound that bad to me compared
16 to what we're doing with mammography and where we've
17 come and where we're going. I don't think you can
18 jump to say -- I mean, I think I agree with all your
19 other things here but I would be hesitant to say
20 that's too high until we have the data because it
21 doesn't sound that bad unless it impacts those single
22 two patients where there are those two false

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1 positives.

2 DR. IBBOTT: Yes, Dr. Ferguson.

3 DR. FERGUSON: Speaking of the labeling,
4 I'm looking here and I'm sorry. I apologize. I have
5 gone through here several times -- not talking about
6 the advertisements but the manual that you have --
7 looking for clear definition of what we saw on the
8 slides which is what I think should be somewhere in
9 here up front, and that is the two slides which we
10 showed about what you must do and what you must not do
11 to use this device. Is it somewhere in here?

12 DR. IBBOTT: You're talking about the
13 always and never rules?

14 DR. FERGUSON: Yes.

15 DR. O'SHAUGHNESSY: I agree it's very
16 important. We're looking for the advice of the panel
17 on this issue and labeling in general. I should
18 comment that particular situation is at the front of
19 your Tab 4 where we've got preliminary warnings and
20 poshuns that would be given to the radiologists.

21 That's where in our mammography product we
22 typically -- these are gone through during your

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1 training session to make sure that the information
2 gets across. Again, we would look to work with FDA
3 with your advice from the panel to come up with
4 appropriate labeling for the device to affect both the
5 manual and any advertisement labeling. That is part
6 of what the job is when we finally work with FDA and
7 get a final labeling for the device.

8 DR. SOLOMON: Two other quick questions on
9 the labeling. One is whether vendors matter. I mean,
10 you have two vendors. There are several others out
11 there and whether or not there's any impact on your
12 system. The second one, as far as labeling goes,
13 whether or not there's an optimal slice thickness and
14 whether or not that should be stressed because maybe
15 the protocol should be changed to optimize your
16 system.

17 DR. O'SHAUGHNESSY: I can answer that at
18 the high level. If you want to go into more detail, I
19 have the technical people here. Although at the five
20 sites we chose to select cases for the regulatory
21 study, they happened to have scanners from the two
22 vendors mentioned, GE and Toshiba, are separate

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1 database cases that was gathered for training the
2 algorithm has representations from all the major CT
3 vendors.

4 In addition, as part of the approval for a
5 CT machine there are very rigorous controls on the
6 quality of the images. Those type of controls more
7 than adequately make sure that the images are adequate
8 for CAD. I believe that's okay. The second question
9 again? I'm sorry.

10 DR. SOLOMON: Optimal slice thickness and
11 protocol design for optimizing your system.

12 DR. O'SHAUGHNESSY: Right. Because the
13 system was designed to address the issue, especially
14 in an information overload situation, we focused the
15 development of the algorithm for slices of 3 mm.
16 collimation or less.

17 In fact, the system won't process CT
18 images unless they have collimation less than that.
19 Part of it is that's where radiologists are most
20 likely to miss. The other factor is it's a more
21 volumetric description of the lung and so the
22 algorithm is designed to perform in that environment.

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1 DR. TRIPURANENI: I heard Dr. Emily Conant
2 loud and clear that it's not our business to actually
3 decide how the user is going to use the system, but I
4 think I have to agree with Dr. Ferguson. I really
5 would like to see in big letters always and never
6 somewhere loud and clear.

7 When you look at this fancy color
8 graphics, for somebody not paying attention it looks
9 like you can push the bottom and the machine is going
10 to tell you everything even though it says "improves"
11 and all those things but I think those two points need
12 to come out loud and clear.

13 DR. STARK: Is there anything in here to
14 give comfort to a radiologist once this product is
15 approved for not buying it? Is there any
16 justification for not feeling bound to use this in
17 every patient whether they have pneumonia, they are in
18 for a car accident, follow-up on a pleural effusion?

19 I'm wondering what type of marketing
20 pressures that we haven't yet seen are going to drive
21 people to feel that they will be left as a wounded
22 calf behind the herd for the malpractice lawyers if

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1 they don't take on the burden of using this product
2 for every CAT scan done in America after the FDA gives
3 this it's imprimatur.

4 DR. CASTELLINO: I thought I got two
5 questions there. One might be, I think, if you have
6 this in your department would you choose to use it on
7 patient A and not on patient B. If they meet the
8 technical requirements, the CAD works in the
9 background.

10 I think it takes an average of three to
11 five minutes to process the images for the CAD
12 results. If you're reading in a standard fashion,
13 which is not really that much on line, the CAD
14 information will be available to you. You can choose
15 to use it or not to use it.

16 My suggestion as a radiologist is if it's
17 there and you think it's worthwhile since you have
18 acquired the technology, you probably should use it in
19 every case but this is up to definitely the person who
20 wants to use it.

21 The second question is a little more
22 difficult to address. I think your question is really

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1 saying if I don't have one should I get one. Our
2 experience with mammography and, Emily, I hate to go
3 back to that but I guess I have to, is that the
4 utilization of CAD mammography, which has been
5 approved five and a half years ago or more, has been
6 relatively slow.

7 I mean, there are many mammography
8 practices that don't have it. In fact, apparently you
9 don't have it. I don't think this is going to force
10 radiologists to get it or not to get it. Just like a
11 16-channel CT scanner is not a necessity if you're
12 doing CT if you have an 8 or a 4, and some people
13 still have a single slice scanner.

14 Or having all the probes and ultrasound
15 machine or having all this or all that radiology
16 programs make decisions on what technology they wish
17 to hire. If they think this is valuable, it will help
18 them in their practice, they will acquire it. If they
19 don't think it's any good, they won't. I think the
20 marketplace will decide.

21 DR. STARK: Shouldn't the labeling of
22 products like this -- this is perhaps a broader

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1 question but I think it pertains here -- contain
2 disclaimers so that someone does not make inferences
3 about the standard of care or what is the required
4 minimal diligence of a physician or a hospital who
5 chooses not to be an early adopter of this technology.

6 DR. O'SHAUGHNESSY: I think that would be
7 up to the panel to discuss. Again, if appropriate
8 labeling is found to be important for this product,
9 then, you know, we'll work with the FDA to include it.

10 DR. KRUPINSKI: Sort of a tangential
11 question. With mammography now when you use CAD you
12 get extra reimbursement above and beyond. Do you
13 foresee this happening with this as well?

14 DR. O'SHAUGHNESSY: I think it's a little
15 early at this stage of this technology to figure out
16 what the reimbursement situation will be.

17 DR. IBBOTT: Let's move on then -- oh,
18 sorry. Go ahead.

19 DR. CONANT: Can I ask just a real quick
20 technical question? Maybe this is very naive and I
21 didn't understand your illustrations but does the
22 algorithm that analyzes the images, does it come -- I

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1 guess can I hook up lots of scanners to it? Is it one
2 box for each scanner or is it one box for each
3 department? I know there are issues with mammography.
4 I'm just curious.

5 DR. O'SHAUGHNESSY: In this situation
6 depending on how many CT images you are going to feed
7 through, the fact that we've utilized the DICOM
8 standard means it's just an appliance sitting on the
9 network so you just push them from any scanner
10 available in your system and as long as you don't
11 exceed the computing capability of the computer to
12 keep up with your case load, there is no restriction.

13 DR. IBBOTT: Well, that's brings us to the
14 question of the training program, No. 3. Please
15 discuss whether the sponsor's proposed training
16 program for radiologists is adequate. If not, what
17 other training would you recommend? I would like to
18 start by asking my question about that. I couldn't
19 find anything in the material here that provided a lot
20 of detail about the training.

21 In particular, how long the training is
22 and how closely supervised it is. You presented a bit

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1 more during your presentations but I wasn't sure if
2 that was the type of training you would propose for
3 customers or if that was training for the people who
4 were doing the evaluation.

5 DR. O'SHAUGHNESSY: I think that is a
6 great issue and good question to bring up. We didn't
7 have the formal training program written up at the
8 time we were submitting the PMA and part of the goal
9 of the training at institutions like Dr. Delgado's was
10 to take a first run at it, assess what changes needed
11 to be made, and then bring that forward.

12 So the format that he described, it was
13 very similar to what we ended up with which is
14 basically depending on the number of radiologists but
15 typically a site would have one of our specialist
16 there for a day. They would work with the radiologist
17 one on one to go over the manual, in particular the
18 algorithm description.

19 Every system that ships will have
20 demonstration cases that are good examples of what CAD
21 marks and what it doesn't mark and the type of false
22 markers they are going to see. And then as the

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1 radiologists get more comfortable with the system, the
2 shadowing that we talked about where they are there
3 available to answer questions like the radiologist is
4 reading on their own but go, "Why is that mark there?"

5 The applications person can answer that.
6 Then in addition to that, the application specialists
7 usually follow up with the site within a week or two
8 or that training to make sure that no other issues
9 have come up. Of course, we are always available by
10 telephone or e-mail if any issues come up. The
11 general outline of the training program is similar to
12 what we do in mammography and we found that to be very
13 effective.

14 DR. KRUPINSKI: As sort of a follow-up,
15 Dr. Delgado said that some people weren't there for
16 the training and then some of the other radiologists
17 trained them. Is that enough? Is that acceptable?
18 Because obviously I wouldn't think they would be able
19 to answer some of the more technical questions so how
20 did you feel about that?

21 DR. DELGADO: That's a good question. We
22 were able to do it quite readily. The training

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1 experience that I had with the application specialist
2 was really just three or four hours in the morning.
3 We had some lunch, they were around for the afternoon
4 and stuck around and watched us read and shadowed us.

5 I think that perhaps that is something
6 that R2 if they want to actually mandate that
7 positions go through the training in that fashion or
8 some kind of course or improvement period. That was
9 not strictly applied in my case as a beta experiment
10 but I see that potentially being used in clinical
11 practice. That is probably a good recommendation.

12 MR. BURNS: A time is not given. You used
13 eight hours. I would suggest a super user trained at
14 the facility and the production of a training CD so
15 that even though you have new radiologists and staff
16 coming on board, training CDs are not that hard to
17 produce and you have your own project. Three to four
18 hours sounds about right to teach someone how to use
19 this work station.

20 DR. DELGADO: I should add that is
21 something that we went through. At least the
22 physicians that did receive the course or the small

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1 introductory application seminar. We did process, I
2 think, relatively about 15 or 20 cases, some of which
3 were provided by R2 and some of which were from our
4 institution. That is some kind of case load that
5 should be either already prefixed or from the
6 institutions. Definitely valid.

7 DR. STARK: I think the most important
8 part of training is going to be identifying what
9 causes these false positives and cataloging them
10 because there are going to be -- there's going to be a
11 pattern and frequency of artifacts or anatomic
12 coincidences that probably the company already has
13 some good idea what they are that are going to be very
14 different than the false positives that we train our
15 residents to recognize in the normal practice.

16 The false positives that the radiologist
17 has to fight off on his own going through the studies
18 are likely to be a very different mix of appearances
19 and locations than the false positives that you are
20 going to see with the device. Also with and without
21 contrast. We have heard that 50 percent of these
22 patients had contrast.

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1 It would be reassuring to actually just
2 see it written down if it's subject to analysis that
3 there are no unique issues post contrast. So in your
4 educational material it might even -- one could even
5 say that someone has to deal with that at the PMA
6 stage but we should see atlases or a CD.

7 It may not be extensive. It might just be
8 10 appearances. You have some examples already in the
9 PMA. These are the things that you can expect that
10 you're going to see 80 percent of the time in
11 eliminating these false positives and let's see the 10
12 or 15 most common variants. A radiologist would train
13 on that in an hour. I think that is an important
14 supplement.

15 DR. O'SHAUGHNESSY: Yeah. I think that's
16 basically -- maybe I didn't explain it clearly enough
17 but that is basically what the manual does is it goes
18 through examples and then we use those demonstration
19 cases that were chosen to give a representative and
20 range of the types of both true and false positives
21 that you see on CAD.

22 DR. IBBOTT: Dr. Delgado, in your

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1 experience with the system did you and your colleagues
2 -- I guess I should ask how long do you feel it took
3 before you became familiar with these sorts of
4 presentations of false positives? Did you find it a
5 complicated process?

6 DR. DELGADO: No, I did not. First of
7 all, one of the comments by Dr. Stark was in my
8 experience in the cases that we processed from our
9 institution many of them were CT contrast-enhanced
10 pulmonary angiography studies. Many of them were
11 contrast enhanced.

12 And we also had many cases that were for
13 lung nodule workups in oncology patients where lesions
14 were detected in chest x-rays. We noticed no
15 significant difference in false positive rates based
16 on contrast or no contrast.

17 DR. STARK: When you say we noticed,
18 you're talking about an anecdote?

19 DR. DELGADO: True. That's my experience
20 and those are my colleagues. As far as the false
21 positives -- is that your question? -- recognizing
22 artifacts or false positives, I believe that -- I

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1 mean, those are normal things that radiologists have
2 to look at now on a daily basis.

3 We have artifacts that are either
4 generated from noise or from post-operative changes,
5 from other technical parameters such as contrast
6 coming into the SBC and being rather dense. I don't
7 see a particular difference that the CAD would present
8 perhaps a false positive mark. The radiologist
9 decision making upon that CAD mark is no different
10 than something that he might have identified himself.
11 That's my perception of the issue.

12 DR. IBBOTT: Any other comments about this
13 question before we go on to the next one? All right.
14 We'll go on to the fourth one.

15 MS. BROGDON: Dr. Ibbott, could I ask the
16 panel to go back to question No. 2, please? Part of
17 our intention in asking this question was that the
18 panel also address the indications for use. Do you
19 believe as a panel that the requested indications for
20 use are appropriate?

21 DR. IBBOTT: And you are referring to the
22 published indications from the sponsor?

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