Transcript of April 16, 2002 Meeting

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11 CENTERS FOR MEDICARE AND MEDICAID SERVICES
12 Medicare Coverage Advisory Committee
13 Executive Committee Meeting
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19 April 16, 2002
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21 Baltimore Convention Center
22 100 West Pratt Street
23 Baltimore, Maryland
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1 Panelists
2
3 Chairperson
4 Harold C. Sox, M.D.
5
6 Vice-Chairperson
7 Robert Brook, M.D.
8
9 Voting Members
10 Leslie P. Francis, J.D., Ph.D.

11 John H. Ferguson, M.D.
12 Alan M. Garber, M.D., Ph.D.
13 Frank J. Papatheofanis, M.D., Ph.D.
14 Thomas Holohan, M.D.
15 Daisy Alford-Smith, Ph.D.
16 Wade Aubry, M.D.
17 Barbara McNeil, M.D., Ph.D.
18
19 HCFA Liaison
20 Sean R. Tunis, M.D., M.Sc.
21
22
23
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1 Panelists (Continued)
2
3 Consumer Representative
4 Linda A. Bergthold, Ph.D.
5
6 Industry Representative
7 Randel E. Richner, M.P.H.
8
9 Executive Secretary
10 Janet Anderson
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1 PANEL PROCEEDINGS
2 (The meeting was called to order at 8:38
3 a.m., Tuesday, April 16, 2002.
4 MS. ANDERSON: Good morning and welcome,
5 committee chairperson, members and guests. I am
6 Janet Anderson, executive secretary of the executive
7 committee of the Medicare Coverage Advisory
8 Committee. The committee is here today to discuss
9 and act upon recommendations from the MCAC Diagnostic

10 Imaging Panel regarding the use of positron emission
11 tomography (PET) scanning technology for the
12 diagnosis and patient management of Alzheimer's
13 Disease (AD) and other dementias. The committee will
14 also continue the discussion from the last executive
15 committee meeting regarding the use of decision
16 modeling in policy making.
17 In evaluating the recommendations
18 presented to you today, CMS encourages the committee
19 to consider all relevant forms of information,
20 including but not limited to professional society
21 statements, clinical guidelines and other testimony
22 you may hear during the course of this committee
23 meeting.
24 The following announcement addresses
25 conflict of interest issues associated with this
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1 meeting and is made part of the record to preclude
2 even the appearance of impropriety. The conflict of
3 interest statutes prohibit special government
4 employees from participating in matters that could
5 affect their or their employer's financial interests.
6 To determine if any conflict existed the Agency
7 reviewed all financial interests reported by the
8 committee participants. The Agency has determined
9 that all members may participate in the matters
10 before the committee today.
11 With respect to other participants, we ask
12 in the interest of fairness that all persons making
13 statements or presentations to this committee
14 disclose any current or previous financial
15 involvement with any firm whose products or services
16 they may wish to comment on. This includes direct
17 financial investments, consulting fees, and
18 significant institutional support.
19 I would now like to turn the meeting over
20 to Dr. Sean Tunis, who will give his opening remarks.
21 Then Chairman Dr. Hal Sox will ask the committee
22 members to introduce themselves and to disclose for
23 the record any involvement with the topics to be
24 presented today. Dr. Tunis.
25 DR. TUNIS: Thanks, Janet. I just wanted
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1 to welcome everybody to another executive committee
2 meeting and thank you for taking the time and trouble
3 to be here today. We have a modestly full agenda so
4 hopefully there will be some time at the end for the
5 committee members to tell various stories. I'm
6 hoping Dr. Garber can tell us about his experience in
7 running the Boston Marathon yesterday. He's alive,
8 apparently he finished, and apparently carried his
9 cell phone along the way just to stay in touch. And
10 I think Randel Richner has a story to tell as well
11 about some adventure yesterday in Baltimore.
12 In any case, I do want to turn the meeting
13 over to Hal Sox to describe the charge for the first
14 part of the committee meeting today.
15 DR. SOX: Good morning. I think we will
16 start by asking the members of the executive
17 committee to introduce themselves and when they do
18 that, when you do that, would you please state any
19 conflict of interest that you have relative to this
20 particular topic. And we'll start with Linda
21 Bergthold.
22 MS. BERGTHOLD: Linda Bergthold, consumer
23 representative, no conflict.
24 DR. HOLOHAN: Dr. Tom Holohan, chief of
25 patient care services, Veterans Health
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1 Administration. No conflicts.
2 DR. GARBER: Alan Garber, Department of
3 Veterans Affairs and Stanford University. No
4 conflicts.
5 DR. ALFORD-SMITH: Daisy Alford-Smith,
6 director of the Summit County Department of Human
7 Services in Ohio. No conflict.
8 DR. McNEIL: Barbara McNeil, Harvard
9 Medical School and the Brigham and Women's Hospital.
10 No conflict.
11 DR. FERGUSON: John Ferguson, neurologist
12 and consultant in private practice. And no conflict.
13 DR. BROOK: Robert Brook, Rand UCLA. I
14 don't think I have a conflict, but I do come from
15 UCLA and a large chunk of the material is from
16 scientists at UCLA as opposed to Harvard, so Barbara
17 has no conflict.

18 DR. AUBRY: Wade Aubry, internist and
19 endocrinologist, the Institute for Health Policy
20 Studies, University of California, San Francisco. No
21 conflicts.
22 DR. PAPATHEOFANIS: Frank Papatheofanis,
23 department of radiology, UCSD. I am a practicing
24 nuclear medicine physician who performs PET scans. I
25 guess a marginal or potentially apparent conflict
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1 would be that our department negotiates with some of
2 the manufacturers who may be involved in the
3 deliberations today, on behalf of the university for
4 the purchase of equipment. Other than that, I have
5 no conflict.
6 MS. RICHNER: Randel Richner, Boston
7 Scientific. No conflict.
8 DR. SOX: Well, our charge today is to
9 either approve the recommendation of the imaging
10 panel or to send it back to the panel for
11 reconsideration. So really, those are the two
12 options. We're here not really to hear new evidence,
13 but to decide whether the process used by the panel
14 meets the expectations that we have set up in our
15 MCAC processes, and insure that there wasn't some
16 serious miscarriage of logic in interpreting the data
17 and reaching the conclusion.
18 So, that's really how we judge the panel,
19 and make a decision whether to approve or not. It's
20 mostly a check on the process of the panel and the
21 notion is that the panel are the people closest to
22 the data and that, the ones that were in the best
23 position to decide what kind of evaluation to provide
24 the coverage group. Our job really, we're experts on
25 process, and we just want to be sure that in coming
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1 to their conclusion, they used appropriate processes
2 both with respect to the consideration and to the
3 interpretation of the evidence. Are there any
4 questions about that? Yes, Wade.
5 DR. AUBRY: I'm wondering if that's a
6 change from the previous process or procedure. It
7 seems to me in past meetings, there have been
8 substitute motions regarding the previous panels'

9 work. Are you saying that basically we either accept
10 the recommendation or send it back, is that true, and
11 is that a change from previous panels?
12 DR. SOX: It's true in the past, I can
13 remember at least one instance where it was my panel
14 that we were evaluating, where we tweaked a word or
15 two, but we're anticipating the time when we will not
16 approve the panel, and simply evaluate the process,
17 and so I would say that we'll have to consider the
18 circumstances as they arise, but in general we are in
19 the process of moving away from really any
20 second-guessing the panel at all other than to
21 evaluate the performance in evaluating and
22 interpreting the evidence. So, that's a bit of a
23 wishy-washy response but we'll just kind of see what
24 happens.
25 DR. AUBRY: Thank you.
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1 DR. SOX: Any other questions? In that
2 case, Frank is going to make the presentation of the
3 process, the data and the interpretation. So, I will
4 turn it over to you, Frank.
5 DR. PAPATHEOFANIS: Thank you, Hal.
6 Hopefully the committee has copies of the summary of
7 the meeting minutes as well as the report by the Duke
8 evidence based practice center, which is this
9 document.
10 I wanted to review very briefly the events
11 of January 10th by starting off with a discussion of
12 process, and then I have a few slides that deal with
13 the actual question at hand and the recommendation
14 that emerged from the deliberations.
15 Before I describe anything else, I wanted
16 to mention that CMS through the guidance of the
17 panel, the Diagnostic Imaging Panel members, was able
18 to obtain the expert advice of three consultants from
19 Harvard, who had expertise not only clinically in the
20 treatment of patients with AD, but also had expertise
21 in the methodologies that were used to arrive at the
22 decisions the panel made. And I was very grateful
23 for their participation and I think that everyone who
24 was present was very appreciative of their thoughtful
25 review of the Duke report, and I think that their

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1 contributions to that session were very meaningful.
2 As you know, AHRQ commissioned the Duke
3 center to prepare a technology assessment. The
4 assessment was performed by a group headed by
5 Dr. David Matchar, who is here in the audience and
6 who I hope we can tap if we have any concerns
7 regarding the details of the model beyond our
8 deliberation. But as you can see, there was a whole
9 host, on the cover page of this document, there was a
10 whole host of individuals who participated in the
11 formulation and in the completion of this study.
12 Likewise, at the rear of this document,
13 there is another list of consultants and peer
14 reviewers that went through the document on behalf of
15 the Duke group, and I think that from my perspective
16 and I think Barbara will speak later, it seemed that
17 they did a very thorough job in assessing the
18 questions that were posed by CMS.
19 So when we met, we started off by using
20 this technology assessment as basically a reference
21 document from which we considered Dr. Matchar's
22 group's analysis and considered the conclusions that
23 were formulated by the analysis. Some of the points
24 that came up during the discussion were specifically
25 related to the notion of the American Academy of
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1 Neurology guidelines for the evaluation or workup of
2 patients with suspected AD. And again, referring to
3 this reference document, you can see where the Duke
4 group broke down the various options that existed for
5 the management of a patient who presented with either
6 early signs and symptoms of the disease, or with
7 first degree relatives or other dispositions that
8 might suggest the likelihood of them developing
9 Alzheimer's disease at some point in the future.
10 The deliberations that we had focused on
11 whether or not that was a reasonable tack to take.
12 We relied on experts, physicians who actually treated
13 patients with disease or suspected disease, as well
14 as the review of the literature, the evidence tables,
15 and the conclusions that came out of the report. So
16 I think that the committee had at its disposal quite

17 a bit of information upon which to make the decision
18 concerning the questions at hand.
19 Finally and not at all unimportantly was
20 the testimony that we heard from members of the
21 audience. There were several presentations that were
22 made by speakers who signed up in advance and had
23 been granted specific time slots to present their
24 evidence on behalf of the use of PET for patients
25 with AD, and there were also individuals who

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1 volunteered and were given permission to address the
2 panel at the time. So I think we had a very
3 comprehensive mix of information sources in the
4 expert testimony of the consultants that were used by
5 our panel, again, both clinicians and methodologists.
6 We had the evidence that the Duke EPC
7 provided in the form of a written report, and
8 finally, we had the input of the members and experts
9 at hand.
10 And so, I think that pretty much wraps up
11 the process of how we arrived at our discussion and
12 how we arrived at the conclusions that we made.
13 I want to flip over to my very brief slide
14 presentation. I don't know how that's going to work.
15 I can see the yellow light already going
16 off.
17 (Laughter.)
18 DR. PAPATHEOFANIS: What I wanted to do
19 was take perhaps five minutes to review in summary
20 the deliberations of our panel and again, review the
21 specific question at hand that we considered. The
22 question that was posed to the contractor, in this
23 case the Duke group, is as stated there: Is the
24 evidence adequate to demonstrate that PET has
25 clinical benefit in evaluating patients with AD?

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1 And this model, as is noted on the slide,
2 was developed by Dr. Matchar and his group and then
3 validated by Dr. Peter Neumann, at the Harvard School
4 of Public Health, and Dr. Neumann was one of the
5 outside experts that we had present at our meeting
6 January 10th. He participated very actively in the
7 discussion and I think did a fine job of addressing

8 our questions regarding the methodologies that were
9 used.
10 To give you a very brief background, once
11 again, we took as our starting point the existing
12 American Academy of Neurology guidelines that
13 recommend treatment with cholinesterase inhibitors
14 for patients with suspected AD. Again, these are
15 patients who have a family history or who have signs
16 and symptoms on physical examination. The
17 meta-analysis that was performed by the Duke group
18 showed the true positive and true negative rate for
19 PET that you see there, approximately 86 and 87
20 percent.
21 We also had very specific wording, and
22 this guideline appears in the technology assessment
23 provided by Duke, that the AAN guidelines do not
24 recommend the use of PET and finally, there is a
25 reference there that is available.
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1 By the way, the minutes of our
2 deliberations are also available on the web, so
3 whoever wants to delve into the details, they are
4 posted.
5 To continue with the background, treatment
6 of patients with AD delays progression by six months,
7 which we felt and we thought was a significant
8 interval, so there is justification from a clinical
9 perspective for the use of the cholinesterase
10 inhibitors. Current drugs are generally believed to
11 have a low risk of side effects, and we spent quite a
12 bit of time discussing these side effects, and the
13 committee was convinced that either the side effects
14 are transitory or they are of such low grade that
15 they don't preclude their use in the majority of
16 patients, I think in over 90 percent of patients.
17 Finally, there are no good data on the impact of PET
18 on the management of outcomes of patients with this
19 disease.
20 To review in a little greater depth our
21 approach, a decision analytic model was developed by
22 the Duke EPC. It considered three different aspects
23 of the disease as I alluded to earlier, that is,
24 patients with mild to moderate dementia from presumed

25 AD, who based on a AAN recommendation, or I'm sorry,
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1 an AAN guideline workup, were thought to be
2 candidates for treatment; patients with mild
3 cognitive impairment or MCI; and then finally, the
4 patients with no symptoms at the time of evaluation
5 but with first degree relatives with a history of AD.
6 The sensitive analyses that we used, and
7 you can see multiple sensitive analyses throughout
8 the document, tested PET and treatment
9 characteristics. The specific end points were the
10 correct diagnosis, and the diagnosis or misdiagnosis
11 that led to the identification of false negatives.
12 The sensitivity analyses were done very
13 methodically and basically there were one-way and
14 two-way sensitivity analyses, wherein the one-way,
15 one variable of interest was kept, was modified
16 whereas all the others were kept constant, but I
17 think the next level of sophistication was in the
18 two-way sensitivity analyses where we see both
19 complication rates and diagnostic efficacy. We found
20 that to be especially useful.
21 So, let me go over a couple of these
22 two-way sensitivity analyses very briefly. The first
23 one covers effectiveness in treatment from 0 to 100
24 percent, and also looks at the complication rate.
25 Now the complication utility is in the Y axis, and
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1 basically the complication rate increases as the
2 number decreases. The treatment efficacy also is
3 displayed the same where the treatment efficacy
4 increases as the number decreases. And what you have
5 here is a baseline or base case, which is very well
6 described in the technology assessment, of a patient
7 who is 76 years old and undergoes diagnosis and
8 presumed treatment according to the AAN guidelines
9 and according to the existing patterns of care that
10 have been expressed to us by clinicians and
11 neurologists for treating these patients.
12 And so what you see here is the result of
13 this two-way sensitivity analysis, and is that the
14 base case falls squarely in the zone corresponding to
15 treat all patients without further testing.

16 The other two-way analysis that I want to
17 very briefly touch on, and obviously this is all
18 explained in great detail in the reports you have
19 reviewed, deals with effectiveness and complications
20 over the current ranges that we're interested in.
21 And again, what you see is the base case or the base
22 line falls well within the treatment of all patients
23 who present with mild dementia. And the complication
24 utility is over 0.99 for the duration of treatment,
25 which means that it's extremely, extremely low.
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1 Basically, the position of the base case
2 in this scenario also confirms that the model, I
3 think, fairly represented what was evident in the
4 published literature and what was derived from the
5 evidence tables. And so our group, the Diagnostic
6 Imaging Panel concluded that PET is not or would not
7 be useful in any of the three diagnostic groups, if
8 you will, that were identified and were carved out in
9 the assessment. The treatments actually become more
10 effective and complications from them are worse in
11 very very few patients.
12 With PET and current treatment options,
13 avoiding unnecessary treatment is associated with
14 denying treatment to patients with AD or who will be
15 developing AD who will benefit from it.
16 Currently, false negatives are worse than
17 false positives, and the basis for that statement is
18 the notion that there is in the cholinesterase
19 inhibitors a relatively effective treatment for
20 delaying the onset of signs and symptoms of disease,
21 and for ameliorating current symptoms. And missing
22 those patients and denying them the opportunity to be
23 treated is tragic from a social ethical human
24 perspective, and based on the 89 percent sensitivity
25 of PET in the situation, the committee felt that
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1 avoiding therapy unnecessarily in these false
2 negatives was not acceptable.
3 The question then for the contractor, is
4 the evidence adequate to demonstrate, and you know
5 that, and you know what our answer is, it was a
6 unanimous no. And there was quite a bit of

7 deliberation by the committee on all points that are
8 associated with this analysis. I can honestly say
9 that we took this fairly carefully. It was the first
10 time that a decision analytic model was being used to
11 really drive the process, and I think we were
12 cautious and really tried to cross our Ts and dot our
13 Is, and I can't overemphasize the importance of the
14 outside contributors.
15 So rather than babble on, if that's
16 adequate, Hal, I think I will stop here and give
17 Barbara a chance.
18 DR. SOX: Great. Barbara, would you like
19 the chance?
20 DR. McNEIL: I would like to just say a
21 word. Frank, I think, summarized it well. A couple
22 of points.
23 The first is that the committee took very
24 carefully two criteria the executive committee had
25 developed initially in its lifetime, that emphasized
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1 that the evidence had to be adequate to determine
2 whether the test provides more accurate diagnostic
3 information and affects health outcomes. And because
4 there had been no data on the impact of tests on
5 health outcomes, the only approach dealing with that
6 was through a model based activity that David and his
7 group did. So that was our underlying modus
8 operandi.
9 And the other point worth mentioning is
10 that the sensitivity analyses that Frank just
11 mentioned, we spent a lot of time discussing the
12 utility scale there which goes from 0 to 100, and
13 this was particularly important. We benefitted a lot
14 from Peter Neumann's expertise in this area. It
15 turns out one of his graduate students had just
16 completed a magnum opus on the summary of the
17 utilities that had been assessed from patients and
18 from their caregivers for a variety of disease
19 states. So he brought to the panel that summary
20 literature which dated back from the late '70s, and
21 it was clear that on the basis of that literature and
22 more current literature as well, that the utilities
23 even for the complications that we're talking about,

24 were very much in the upper 90s, that they in no way
25 could fall much lower than that.
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1 So our conclusion is as Frank said. We
2 also considered carefully the Table 10 document which
3 looked at some nonquantifiable issues that I know one
4 of the outside people addressed.
5 The final comment I would make is a very
6 important one, I think, and it's a little
7 counter-intuitive, and that is that those analyses
8 showed that for testing to be warranted or to be
9 recommended, treatment would have to be considerably
10 better, that is, moved to the left, and complications
11 would have to be really worse. And it was only when
12 that combination, lots better treatment and lots
13 worse complications, that we would be in a situation
14 to flip from the recommendation to one that was test
15 and then on the basis of information from testing,
16 treat.
17 So my summary statement would be that I
18 thought, I have been part of only a couple of panel
19 meetings that we have had and this executive
20 committee as well, but I thought the process was
21 really quite good, Hal.
22 DR. SOX: Perhaps somebody could comment
23 on test performance. You didn't tell us about the
24 studies of test performance, what gold standard was
25 used, the degree to which the results of the PET scan
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1 might have determined whether the patient got the
2 gold standard test.
3 DR. McNEIL: There was a number of
4 studies, Hal, and some of them were flawed with
5 verification bias as you're implying, but the AAN
6 guideline talked specifically about several that used
7 histopathology as the diagnosis. And because of the
8 possibility of verification bias, which David
9 addressed in his report, the importance of
10 sensitivity analyses was really quite critical.
11 But I think that the meta-analysis showed
12 the data that Frank summarized and the bottom line
13 is, it would be very hard to get to a sensitivity
14 higher than the high 80s or low 90s even if you

15 pulled out selectively, and there are some ROC curves
16 that show a few individual cases without sacrificing
17 a lot on the specificity side.
18 DR. SOX: If verification bias were
19 present, it should tend to lead you to overestimate
20 sensitivity and make the situation look better for
21 testing.
22 DR. McNEIL: That's right, so that 87
23 percent that was on the slide, at least from the
24 literature today, is probably pretty good.
25 DR. SOX: So, is there any value of
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1 sensitivity where routine testing would have been
2 appropriate?
3 DR. PAPATHEOFANIS: Not from what the
4 literature showed here. There is also, Hal, to
5 Barbara's point, in figures 5.B through 5.D, a
6 progressive increase in the performance of the
7 medication. It's expressed as a treatment efficacy
8 variation in this case, where what you see is
9 basically as we progress to greater treatment
10 efficacy resulting in higher expected values for
11 these patients. The highest gain is on the order of
12 two to three weeks, which I think very dramatically
13 brings the point of moving the curves around a little
14 bit.
15 DR. SOX: One last question. Did you
16 assume a single value for the pretest probability of
17 AD given the presentation with mild to moderate
18 cognitive impairment and are there some pretest
19 probabilities, relatively low pretest probabilities
20 where testing might make a difference? How did the
21 prior probability --
22 DR. McNEIL: Maybe David could answer
23 that, Hal, but I think it's best summarized actually,
24 without going, well, I guess going to other
25 literature, in the AAN guideline which actually talks
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1 explicitly on page 115, about the impact of pretest
2 probabilities in various situations, and how a
3 variation in the pretest probability would not have
4 changed the conclusions, but maybe David wants to say
5 something.

6 DR. SOX: Did you want to say something,
7 David?
8 DR. PAPATHEOFANIS: There is also the base
9 case; were you going to get into that?
10 DR. MATCHAR: I was just going to comment
11 that the base case, we actually used a relative low
12 prior probability of about 50 to 55 percent,
13 reflecting the fact that even after patients are
14 evaluated clinically, they may still not have AD
15 ultimately, so over that range and even a wider
16 range, there was really no, there was in fact no
17 impact.
18 DR. SOX: Bob?
19 DR. BROOK: Did you look at a base case
20 scenario which basically says that the system right
21 now is incompetent in diagnosing anything that looks
22 like a dementia, let alone AD and if a person just
23 wanted to know, you know, a person could recognize,
24 hey, I'm doing something different, I want a PET scan
25 because I can't get anyone even to do a mini-mental,
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1 find me, follow me, do anything because the average
2 level of care for this constellation of symptoms is
3 just terrible. Did anyone model out the worst case
4 scenario where sort of what is going on in primary
5 care in the United States at the moment?
6 I mean, you were assuming sensitivity over
7 something, and I couldn't get from the material that
8 you sent me what is the assumption about the average
9 level of quality of diagnosing this condition at the
10 moment.
11 DR. MATCHAR: Well indirectly, you can
12 take that from the analysis, because the basic idea
13 is that there is no evidence that PET scanning
14 differentiates a more responsive patient to treatment
15 and that the treatment is relatively benign so at a
16 relatively low or very low prior probabilities,
17 treatment would be a reasonable strategy. We are not
18 dealing with cost issues and some other issues that
19 were outside the purview of this analysis, so if you
20 take that as a given and then you take a low prior
21 probability as we did in the sensitivity analysis,
22 that is that clinicians may be really lousy at

23 evaluating patients with cognitive or possible
24 cognitive impairment, that evaluating them poorly
25 admittedly, we're not advocating that, but evaluating
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1 patients poorly, simply patients who have some
2 cognitive impairment, and then proceeding from that
3 point and saying okay, let's try treatment, empiric
4 treatment. Not a great idea, we're not recommending
5 it, but if you were to take that strategy, then the
6 empiric treatment strategy would be dominant.
7 DR. BROOK: So, let's go over this. If
8 you have an 80-year old person --
9 DR. SOX: Bob, what I would like to do now
10 is just focus on issues of clarification of the
11 analysis and --
12 DR. BROOK: That's what I'm trying to do.
13 DR. SOX: Let me just continue. And to
14 leave other questions really for the discussion
15 period. So continue your line of questioning, but
16 not too long, so we can give a chance for the public
17 to have their say. Go ahead.
18 DR. BROOK: I'm fine.
19 DR. SOX: Alan, a question of
20 clarification?
21 DR. GARBER: David, don't step down yet.
22 I was just a little unclear about how the utility of
23 complications was calculated and I'm not sure I read
24 the report correctly, but it sounds like the reason
25 you get a dysutility is because you no longer get the
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1 benefits of treatment mainly, or was there an
2 additional penalty due to the complications
3 themselves, and how did you model that?
4 DR. MATCHAR: Well, first of all, in
5 generating the model we allowed there to be all kinds
6 of bad things that could happen with treatment. We
7 included the possibility that first of all, that not
8 everybody would have a complication, that there would
9 be a certain probability of having complications.
10 Complications could lead to decreased quality of
11 life, complications could lead to mortality, and
12 complications could lead to actual progression of
13 disease, and we considered that as a possibility only

14 because one never knows that a future treatment may
15 be effective for some people but actually may make
16 some people worse.
17 And so, we really did look at
18 complications as a more general phenomenon, not just
19 this issue of decreased quality of life. But if we
20 only focus on the base case, we're talking about say
21 the 15 percent of individuals who have the
22 complications and then two things happen, one is that
23 they have a transient decrement in quality of life,
24 which in the scheme of utility is relatively
25 minuscule. And the second is the indirect phenomena,
.00031
1 which is that people who had complications were
2 assumed to stop treatment.
3 DR. SOX: Are there any other questions
4 from the panel?
5 The next step then in our deliberations is
6 to hear from members of the audience, and we'll start
7 with scheduled public comments, and Janet is going to
8 say a few words about the ground rules here.
9 MS. ANDERSON: Today's first speaker is
10 going to be Dr. Gary Small, who will be followed by
11 Dr. Silverman, and then the rest of the list is
12 available out on the front table if anybody wants it.
13 I just want to remind our speakers that
14 for the record you will state your name, your
15 affiliation, and disclose any conflicts or other
16 professional information that we should know, and
17 that we are keeping everyone to 10 minutes.
18 DR. SMALL: Thank you, Janet. My name is
19 Dr. Gary Small. I am director of the imaging and
20 genetics at UCLA, part of the Alzheimer's Disease
21 Search Center. I am also a member of the American
22 Academy of Neurology practice parameter committee on
23 dementia, and I chair the PET subcommittee for the
24 neuroimaging work group for the Alzheimer's
25 Association.
.00032
1 I can add that that subcommittee is in
2 favor of the use of PET to assist in the early
3 diagnosis of dementia, and also that the Alzheimer's
4 Association is a national organization that

5 represents the millions of caregivers and family
6 members who are dealing with this devastating
7 illness.
8 In terms of apparent conflicts of
9 interest, I have done research on PET scanning, taken
10 care of Alzheimer patients for nearly 20 years now,
11 and also used PET in my clinical care of patients,
12 and also consult with the several companies that make
13 cholinesterase inhibitor drugs for AD.
14 Dementia and AD affect about 8 percent of
15 people 65 years or older. Four million patients in
16 the U.S. have an annual estimated cost to the United
17 States of over $100 billion. There is compelling
18 evidence that patients with probable AD benefit from
19 cholinesterase inhibitor treatment, and they benefit
20 in terms of their mental function, their behavior,
21 the activities of daily living and the caregiver
22 burden. There is also no evidence to treat patients
23 without a specific diagnosis with any pharmacologic
24 agent in this area or certainly in any area of
25 medicine.
.00033
1 A definition for dementia, acquired
2 syndrome of decline in memory and at least one other
3 cognitive function such as language or other mental
4 domains sufficient to affect daily life in older
5 persons. So in a sense, a dementia diagnosis is a
6 severity diagnosis, because we know these are very
7 subtle changes that progress gradually over the
8 years.
9 If someone has dementia, there is a long
10 list for the differential diagnosis, but just to
11 summarize it as we heard earlier, about 55 percent of
12 cases are going to be AD and about 45 percent will be
13 some other condition. It could be a
14 neurodegenerative disorder, it could be other
15 conditions, it could be thyroid illness and so forth.
16 If we can accurately diagnose this 55 percent, then
17 there is going to be a 45 percent savings in terms of
18 side effects or other risks in treating people who
19 don't have the disease that we're concerned about.
20 As we have heard just a moment ago, there
21 are issues in terms of what's going on in the

22 community with primary care physicians in the
23 challenges with the dementia diagnosis. Primary care
24 physicians care for most patients, about 65 percent,
25 who have dementia. Usually they do not use the
.00034
1 standard American Academy of Neurology diagnostic
2 criteria. A recent study found that only 40 percent
3 of primary care physicians, compared with 97 percent
4 of experts, even knew that AD was the most common
5 cause of late life dementia. Misdiagnosis is
6 prevalent.
7 Callahan and associates did a recent study
8 where they found that 75 percent of patients with
9 moderate dementia were not diagnosed, and when you
10 get to mild dementia, it's as high as 97 percent. We
11 know that under recognition of dementia leads to
12 consequences, higher hospitalization rates, emergency
13 room visits, motor vehicle accidents, medication
14 errors and mortality.
15 The current diagnostic assessment is
16 summarized here and there are different iterations of
17 this, such as what we see with the American Academy
18 of Neurology, where there's a history, talking with
19 caregivers, looking at the course of the illness and
20 exam, standardized mental tests, functional
21 assessment and laboratory assessment, primarily used
22 to rule out other treatable illnesses aside from AD.
23 What would be some of the benefit of early
24 diagnosis? This is just one example from a treatment
25 study of one of the cholinesterase inhibitor drugs
.00035
1 and there are similar data like this. If you look at
2 the vertical axis, this is improved cognition going
3 up, and this is number of months in the study. This
4 is a double blind controlled study and this is the
5 active drug group showing better cognition after six
6 months, the placebo group showing a decline. And
7 after six months, they put all the placebo patients
8 onto active drug, and you can see there is some
9 improvement but never quite to the level that
10 patients might have been had they started earlier on
11 the cholinesterase inhibitor therapy.
12 Now certainly there are issues about trial

13 design and dropouts and so forth, but this is
14 something that has been replicated, and it suggests
15 one explanation and that is, if we start people
16 earlier, we're going to have better benefit.
17 We've heard about some of the data as far
18 as clinical assessments, and the American Academy of
19 Neurology panel after looking at 7,000 articles in
20 the literature, found only one study with Class I
21 evidence looking at early diagnosis of dementia using
22 the so-called conventional clinical approach. And
23 this is multiple clinical assessments over years.
24 They had 130 autopsy confirmed outcome cases.
25 Diagnostic accuracy included sensitivities in the 83
.00036
1 to 85 percent range, and specificities in the 50 to
2 55 percent range.
3 The study that Silverman, et al., did
4 recently looking at just a single baseline PET scan
5 in 284 patients and of these, a comparable number had
6 autopsy outcome. We can see higher sensitivities and
7 specificities, sensitivities in the 93 to 95 percent
8 range, and specificities in the 73 to 78 percent
9 range. So PET assists with early dementia diagnosis;
10 AD is prevalent, it's costly but can be treated,
11 especially early on.
12 The current approach to the dementia
13 diagnosis involves multiple costly assessments
14 performed over years. PET provides early positive
15 differential diagnosis for Alzheimer's and other
16 dementias, and the classic Alzheimer's PET pattern
17 can appear years before the disease can be confirmed
18 clinically.
19 Here's just one case example, we have
20 many. A patient who came to our UCLA memory clinic,
21 she had been diagnosed with depression after over two
22 years of multiple evaluations including serial MRI
23 scans. We finally gave her a PET scan and you can
24 see the deficit in the parietal area. We started her
25 on a cholinergic treatment and actually both her mood
.00037
1 and her cognitive symptoms improved within a matter
2 of a month.
3 We have heard about the treat all scenario

4 and that there is no downside to cholinesterase
5 inhibitors. I would just like to raise a couple of
6 points in that matter. First, the data from clinical
7 trials do show side effects that you can see; for
8 example, rates of nausea ranging from 5 to 50 percent
9 in active drug groups, compared with 3 to 28 percent
10 in placebo groups. The dropout rates in the clinical
11 trials due to adverse events range from 7 to 32
12 percent in the active drug group versus 1 to 8
13 percent in placebo groups.
14 And these are clinical trials where
15 patients are relatively healthy. In clinical
16 practice our patients have multiple medical
17 conditions, which increases the side effect rate.
18 And there are certainly multiple case reports of more
19 serious side effect such as convulsions, violence,
20 mania, hepatitis, and other conditions.
21 What would be the practical consequences
22 of improved diagnostic accuracy? We'd have more
23 accurate diagnostic information education, that would
24 reduce family and caregiver burden. It's not just
25 getting people on the right treatment. There is a
.00038
1 decreased likelihood of repeated diagnostic
2 assessments and testing. We have heard about this
3 idea of AD labeling and the problem with that. A
4 recent study actually showed that when patients and
5 family members got the diagnostic label, that it
6 actually improved the caregiver attitudes and the
7 interactions with patients.
8 Also, information about the disease
9 improves quality of life for the patients, for the
10 family members, and Mary Mittelman's group actually
11 showed that it delayed nursing home placement by as
12 much as a year.
13 Other practical consequences, early
14 accurate diagnosis and treatment will maintain
15 patients at higher levels of functioning, leading to
16 fewer physician and hospital visits. It will reduce
17 caregiver burden, it will delay nursing home
18 placement, we've already heard about that. It
19 reduces the use of other psychotropic medications.
20 The diagnosis of dementia is missed in a

21 large proportion of our patients. Current clinical
22 approach to dementia diagnosis is often inaccurate.
23 It involves multiple examinations over years. The
24 current treatments are effective but they do have
25 side effects, so we want to find the right patient
.00039
1 group to treat. PET adds to the current clinical
2 approach by improving this early diagnostic accuracy
3 and reducing the need for repeated clinical
4 examinations.
5 Finally, when should PET be used? I think
6 it should be used to assist in the early diagnosis of
7 dementia. And what would be the effect of using PET?
8 We would have more accurate earlier diagnosis, there
9 would be better treatment outcomes, there would be
10 fewer unnecessary clinical assessments, and we would
11 have earlier treatment when drugs are most effective.
12 Thank you very much for your attention.
13 DR. SOX: Thank you, Dr. Small. We have
14 time for a couple of brief questions and brief
15 responses by way of clarification. Barbara.
16 DR. McNEIL: I have one question and it
17 may be moot. Is somebody presenting from the
18 Alzheimer's Association? Can you reconcile your
19 statement that the Alzheimer's Association recommends
20 PET with the written statement that we just got
21 staying that it doesn't?
22 DR. SMALL: My statement was on behalf of
23 chairing the PET subcommittee for the neuroimaging
24 work group. This is a committee that right now is
25 meeting, we're deliberating. We have a draft of a
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1 report that should be available very soon, before the
2 World Alzheimer's Congress when we're going to be
3 reviewing that.
4 DR. McNEIL: So it's not discordant then,
5 it just hasn't bumped all the way up to the top.
6 DR. SMALL: It's a more recent
7 deliberation.
8 DR. SOX: Other questions for Dr. Small?
9 In that case, thank you very much, and we will move
10 along. Our next speaker is Daniel Silverman, from
11 UCLA, and you can introduce yourself and remind us of

12 any conflicts you have.
13 DR. SILVERMAN: Thanks first to Ms.
14 Anderson and the committee for the opportunity to
15 present here today. I am Dan Silverman, from the
16 UCLA school of medicine, and I have no financial
17 conflicts of interest in any firm representing
18 anything to do with today's topics.
19 So the question before the committee today
20 is, should this executive committee ratify the
21 recommendations of the Diagnostic Imaging Panel? And
22 I'm going to be discussing numerous failures in the
23 process of the Diagnostic Imaging Panel that would
24 preclude that from happening.
25 We would all like to have had an outcome
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1 that we could be confident in from the Diagnostic
2 Imaging Panel's proceedings but unfortunately, the
3 truth of the matter is that we can't be because of
4 many of these failures. I will focus first of all on
5 failures in procedure, and these fall into three
6 major categories, two of which I will talk about now.
7 First, the imaging panel actually failed
8 to vote on the question that they were asked by the
9 executive committee to address and that they had
10 agreed to address, and so whatever they ended up
11 deciding actually is only minimally relevant to the
12 question that was posed to them by CMS and the
13 executive committee, and the question they actually
14 agreed to address.
15 And then secondly, that they failed to
16 follow the approved guidelines for evaluating
17 diagnostic tests as have been explicitly described by
18 the MCAC executive committee earlier in that year.
19 So, I will begin with the first of these
20 failures, that is, on the voting question issue, and
21 I will trace back to where this first began to be
22 formulated somewhat concretely, and that really was
23 in May of 2001 when CMS submitted a formal request to
24 the Agency for Health Care Research and Quality to
25 produce a quality assessment, quote, on the use of
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1 PET and other neuroimaging techniques in the
2 diagnosis and management of dementia.

3 And then secondly, a month later this
4 executive committee actually met to discuss, quote,
5 the contents of and framing the questions for a
6 future presentation of neuroimaging for dementia, to
7 be presented to the Diagnostic Imaging Panel.
8 So it was clear that that was supposed to
9 be the proceeding that led, gave specific direction
10 to what it was that the Diagnostic Imaging Panel was
11 supposed to address.
12 And then during the executive committee
13 meeting, the question was actually extended somewhat
14 as the refined their review of what the question
15 should be, and so they also addressed the issue of
16 patients who do not yet meet the clinical criteria
17 for dementia. And one expert on AD was called to
18 provide input, and that's Dr. Marilyn Albert who we
19 also have the benefit of hearing her expertise this
20 morning.
21 She stated with regard to the potential
22 value of the preclinical patients being tested,
23 quote, people who have complaints and concerns about
24 their memory problems are going to clinicians for
25 evaluation, and those people are very difficult to
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1 evaluate. And she went on to say, even the
2 treatments we have now do slow up the disease, and
3 it's pretty clear that the earlier you take them, the
4 more beneficial they are. So if you could identify
5 people in the preclinical phase of the disease, then
6 treatment intervention would be beneficial and there
7 would be a great worth in that.
8 And that was actually concurred upon by
9 the executive committee and it was done so despite
10 that it was acknowledged that there was no direct
11 evidence for treating these patients, because all the
12 studies had actually been done with patients who had
13 probable AD and in one case, also possible AD, but
14 that based on the strength of the logic of the
15 connections that had been established between getting
16 to patients who are earlier in the process and the
17 more benefit the earlier they were, that it was
18 considered to be acceptable if you could find those
19 patients, that that would be accepted as patients who

20 could benefit from treatment.
21 And so, the Diagnostic Imaging Panel
22 convened on January 10th to carry out its charge, and
23 the voting question which was set forth in the
24 panel's information packet and stated at the outset
25 of the meeting was, as Dr. Papatheofanis also pointed
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1 out, is the evidence adequate to demonstrate that PET
2 has clinical benefit in evaluating patients with
3 suspected AD, which is a very good translation of
4 what CMS and the executive committee had asked them
5 to do, as long as you recognize that suspected AD
6 includes a wide range of people who had been
7 discussed in those meetings, that is, patients who
8 have dementia; patients who are preclinical both with
9 MCI and also as was discussed, who don't meet the
10 criteria for MCI but have age associated memory
11 impairment; and patients who have dementia can fall
12 in categories of those who have possible, probable
13 AD, and those who don't have possible or probable AD.
14 But this Diagnostic Imaging Panel neer
15 voted on the voting question. Why not? Well, in the
16 final minutes of the meeting on January 10th, the
17 voting question was withdrawn and another motion was
18 made, you can find this on page 184 of the
19 transcript, to vote on a substitute question. But it
20 was unclear even to the person making the motion,
21 exactly what that substitute question should be.
22 And after what amounted to seven or eight
23 pages in the transcript, about five to ten minutes of
24 discussion, the discussion culminated in the
25 following way, with the chairman, Dr. Papatheofanis
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1 saying, are you recommending then in the wording of
2 the voting question that we change the word suspected
3 to possible or probable AD.
4 Dr. Albert responded first. She said,
5 well, I think so. And Dr. Papatheofanis said Kim,
6 because he was the person who made the initial
7 motion, and he said I'm just trying to differentiate
8 this from MCI so we don't sort of overstep what has
9 very little information which you notice, goes
10 directly against essentially the spirit of what the

11 executive committee had asked them to address. But
12 then Dr. Papatheofanis says, would you prefer
13 possible probable.
14 And I just wanted to take a moment to say
15 what was really happening here is after a year and a
16 half process and intensely over the last 11 months,
17 where there was much work being done by many people:
18 By CMS; by the Diagnostic Imaging Panel; by the group
19 at UCLA who initiated the coverage request and
20 provided documentation; by the Duke group who
21 actually did a very elaborate model on this, for a
22 carefully crafted well-defined question about what it
23 is they should be addressing. They ended up in the
24 final minutes of the meeting basically turning it
25 into what the preference was of a person who made a
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1 motion, disregarding all that had happened before
2 that point.
3 Okay. Since the time is short, I will
4 turn now to a second category, and that was failure
5 to follow approved guidelines for evaluating
6 diagnostic tests as has been described by the
7 executive committee. As stated during the executive
8 committee's meeting on June 14th, the MCAC criteria
9 is applied to this issue, and these criteria in broad
10 form, which were outlined in the early part of 2001
11 and ratified in May of 2001, would involve examining
12 the test accuracy, examining the impact of improved
13 accuracy on management, and then the impact of change
14 in management on health outcomes.
15 And as you heard several people discuss,
16 there was no question about the high accuracy of PET.
17 It was estimated by our group to be 85 percent, it
18 was estimated by the Duke group to be 87 percent
19 overall, given the prevalence that was estimated, and
20 it was in fact one of the four outcome measures of
21 the Duke group that was looked at was diagnostic
22 accuracy that PET was a clear winner on, if you
23 included that in your evaluation.
24 Also as you heard many people testify
25 today, there was no question on the impact of change
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1 in management on health outcomes. If patients are

2 properly treated, they do much better keeping them
3 out of nursing homes, for example, anywhere from six
4 months to 30 months depending on which studies you
5 look at.
6 So the only question remaining was to look
7 at what the impact of improved accuracy on management
8 would be, and that was never examined by the Duke
9 group. There are several ways in which you could do
10 that. One of them would be to actually consider
11 empirical data on the effect of diagnosis on
12 management that actually occurs. You could look, for
13 example, when physicians get a diagnosis of possible
14 AD, how often do they actually treat patients with
15 the cholinesterase inhibitors. And likewise with
16 probable AD and likewise when they have mild
17 cognitive impairment, and you could either get
18 empirical data or model how that would change if in
19 fact they had additional information from say a PET,
20 when they had evidence that actually in the brain,
21 the Alzheimer's type changes had already begun to
22 occur. But they didn't do that.
23 Another thing they could have done is to
24 consider what the impact should be based on the
25 professional organizations' guidelines as Dr. Small
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1 reviewed, in which they state that in patients who
2 have probable AD should be treated, and that there is
3 no evidence to support treatment of any other group
4 of patients. But they didn't do that either.
5 And they didn't do what often is done,
6 which is just to make an assumption that you will
7 treat patients according to what their diagnosis is.
8 This for example happened when PET was being
9 considered and passed a couple years ago for staging
10 lung cancer, where if you have a patients where you
11 start off with a Stage I lung cancer, and the PET
12 finds a distant metastasis, which makes them Stage
13 IV, you don't treat them like a Stage I anymore, you
14 treat them like a Stage IV, and if you don't find
15 that distant metastasis, then you do the surgery to
16 cure them by treating them as a Stage I. But that
17 wasn't done either.
18 What was done actually is that the Duke

19 group substituted a hypothetical approach without
20 providing any literature documented empirical
21 evidence to support it.
22 And then finally, I will turn to failures
23 in analysis -- well, actually my light is turning
24 yellow, and since I have time to make a conclusion, I
25 will just do this very briefly and say that although
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1 there was a two-way sensitivity analysis, almost half
2 of the cases that you see in green here that could
3 occur, were cases in which PET would win. And you
4 did hear Dr. McNeil and Dr. Matchar at the time say
5 that you would have to have a substantial dysutility
6 to increase, but what they didn't point out is that
7 it would take actually a very small dysutility if you
8 decreased estimate of efficacy.
9 And if you look at the Duke model and how
10 they actually estimated the baseline efficacy case,
11 this occurs on pages 33 and 35 of the model, there is
12 only one paper that was used to estimate the
13 efficacy. And if you look at the 99 percent
14 confidence intervals in that paper, the efficacy
15 actually would range anywhere from .98, all the way
16 at this end, to .58. So if we just take something
17 like halfway between, it would take a very small
18 efficacy change to create a very small dysutility
19 that is needed to actually get to the area that PET
20 wins. And this committee, the Diagnostic Imaging
21 Panel just did not consider fully the green area, to
22 put it in simple terms.
23 So, conclusion, although the central
24 question that CMS and the executive committee asked
25 the Diagnostic Imaging Panel to assess was properly
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1 slated by the panel staff to be the voting question,
2 it was never voted upon and a different voting
3 question driven by different assumptions, assumptions
4 that were contrary to what the executive committee
5 had charged them with, was substituted in the final
6 minutes of the meeting, resulting in a failure to
7 adequately address the central question.
8 Secondly, the Duke center model didn't
9 meet the needs of the Diagnostic Imaging Panel for

10 addressing the question fully because they didn't
11 address that central middle issue, and as a
12 consequence, the panel felt that it had insufficient
13 evidence available to it with which to support the
14 Medicare coverage request. The evidence does exist,
15 it just wasn't given adequate consideration.
16 So in answer to the question we started
17 with, should this committee ratify the findings, the
18 answer is no, and I will refer you then to the
19 handout to what it is that we recommend actually that
20 CMS do. Thank you for your time.
21 DR. SOX: Thank you very much, Dr.
22 Silverman. Why don't you stay up at the mike in case
23 somebody has some questions for you. Does anybody
24 have any questions of clarification for
25 Dr. Silverman? Yes, Tom.
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1 DR. HOLOHAN: Doctor, in the slides you
2 presented, you quote Dr. Albert, and tell me if I'm
3 reading into this an implication that's not there.
4 But the quotations that are provided give me the
5 impression that you believe that she supports earlier
6 diagnosis. For example, quote, if you could identify
7 people in the preclinical phase, treatment
8 intervention would be beneficial, there would be
9 great worth in that. That's difficult for me to
10 understand considering the April 16th letter from
11 Dr. Albert, who clearly states that speaking on
12 behalf of the AD Foundation, she believes that at the
13 present time, PET is an experimental procedure.
14 So, it seems to me this is not exactly the
15 position that she took when she spoke to us, nor that
16 she has taken in writing.
17 DR. SMALL: These are actually easy to
18 reconcile. The second point you made is what she is
19 saying is the position of the Alzheimer's Association
20 overall. The first point, the point that is actually
21 in my presentation, is the proceedings of the
22 executive committee to decide what would be
23 considered to be reasonable evidence on which to base
24 whether PET would be considered to be valuable, and
25 it was being acknowledged that although it would be
.00052

1 very valuable to find patients who are at an earlier
2 stage than you can make the diagnosis accurately
3 where you are just relying on clinical evaluation,
4 that there was no direct evidence because randomized
5 control trials haven't been published yet looking at
6 those patients, but the strength of the evidence was
7 so strong that if you treated patients earlier in the
8 course of the disease that they would do better, that
9 it was worth evaluating patients to see if you could
10 find those patients who are early.
11 And there is at least six years of very
12 strong evidence in PET that you could find those
13 patients years before you could make the diagnosis
14 accurately by clinical evaluation alone.
15 DR. SOX: Yes, Frank.
16 DR. PAPATHEOFANIS: Very briefly. Just to
17 sort of clear the record a little bit for the panel,
18 if you refer to the minutes and the final panel
19 recommendation, you will see the items that we voted
20 on, and I think the items we voted on were clearly
21 the ones that we were charged to vote on. We also
22 had Sean sitting there beside us, clearly asked and
23 I'm sure the minutes will reflect this, whether or
24 not we had addressed the Agency's concerns and
25 whether our deliberations had met with their
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1 agreement.
2 So I think clearly the questions that we
3 were posed were addressed and were voted on.
4 DR. SILVERMAN: Can I comment on that?
5 DR. PAPATHEOFANIS: The other comment I
6 want to make, and this is just a very brief one, is
7 that we have seen two speakers now who are making a
8 strong point that the earlier we treat patients, the
9 better the diagnoses for addressing patients with
10 presumed disease, the better off they will be. I
11 don't think anyone in this room could agree any
12 stronger than I do. I think that what we learned
13 from the evidence was that PET isn't there and it's
14 still, the evidence wasn't there to say that that is
15 the technology that will provide that.
16 DR. SOX: Okay. We'll have a chance, Dr.
17 Silverman, to get into a discussion during the

18 discussion period. I would like now to try to keep
19 things mostly to questions of clarification. So,
20 Bob.
21 DR. BROOK: I'm trying to sort this out in
22 clarification. The first question is whether this is
23 a routine thing that ought to be done, and I think
24 that's what the voting panel has done, but I was
25 curious when I heard your comment here. This is a
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1 patient who obviously presents because there is a
2 problem with memory or something, and the doctor,
3 presumably a good doctor, doesn't think there's
4 adequate evidence to justify prescribing for some
5 reason and wants to do a PET scan on that patient,
6 which let's say is one-half of one percent of all
7 people that doctor sees, because that's where we are
8 at right now. Did the panel think about this case,
9 is this one of the cases that was considered?
10 DR. PAPATHEOFANIS: It was, and it's in
11 the language that precedes the description of the
12 motion.
13 DR. BROOK: And even after considering
14 this case -- so you considered explicitly this
15 problem?
16 DR. PAPATHEOFANIS: Not explicitly, but
17 something in the vicinity of a patient like this.
18 DR. BROOK: And where the PET is being
19 used not to rule out AD but rule it in in a confusing
20 patient, like the clinical example that you saw of
21 somebody that is confusing even the best
22 diagnosticians in the land and PET is being used to
23 rule it in.
24 DR. PAPATHEOFANIS: We didn't have the
25 best diagnosticians in the land but the average.
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1 DR. BROOK: Okay.
2 DR. SMALL: Actually, the committee
3 explicitly failed to look at this case. You can find
4 this in the final minutes of the transcript, in which
5 it was pointed out that they never even looked at the
6 case and never voted on the case of patients who had
7 a clinical criteria for dementia but were thought not
8 to have AD, that the evidence wasn't strong enough to

9 diagnose them with possible or probable AD. And the
10 question was raised at that point, what are you going
11 to do about the fact that we're charged with the
12 committee to answer that question and you never
13 answered it, and then, a movement was made to adjourn
14 at that point.
15 DR. SOX: Okay. I just want to remind
16 everybody, just so we try to keep things orderly,
17 let's try as much as possible to stick with questions
18 for the speaker, and then we can get into discussion
19 amongst ourselves at the appropriate time. Leslie,
20 did you have a question?
21 DR. FRANCIS: This may be that I'm just
22 foggy from a night in the Atlanta airport so, I
23 wanted you to say again for me what you understand
24 the difference to be between your slide that was the
25 language actually voted on and the language you
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1 wanted the panel to have voted on, the difference,
2 that is, between suspected and possible or probable.
3 Exactly what group of patients would have been
4 handled but wasn't, or could you just put up the two
5 slides.
6 DR. SILVERMAN: That is a very important
7 question and I am glad you gave me a chance to
8 clarify that. So, the question that was supposed to
9 be voted upon was suspected AD, and it was clear from
10 the proceedings of the executive committee last year
11 that that included several groups. It includes
12 people who have dementia and it includes people who
13 don't yet have dementia but probably have or may have
14 incipient AD, they just don't meet the criteria of
15 severity yet enough to call it a dementia. And in
16 mild cognitive impairment, at least 50 percent of
17 those people, according to the American Academy of
18 Neurology papers reviewed, would actually have
19 incipient AD.
20 The Duke center actually estimated 80
21 percent of them have incipient AD. It would also
22 include, and Dr. Albert talked about this group too,
23 patients who don't strictly meet the definition of
24 mild cognitive impairment but who do have memory
25 complaints, what we sometimes call age associated

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1 memory impairment, and at least 10 percent of those
2 people after the age of 65 have incipient AD in their
3 brains.
4 And it would include people who have
5 dementia, of course, who have the diagnosis of
6 possible or probable AD, which based on the
7 inadequate sensitivity and specificity of clinical
8 evaluation, about 75 percent of them actually have
9 AD. And it would include people who have dementia
10 who aren't thought to have AD, and based on the
11 inadequate sensitivity and specificity, actually
12 about 15 percent of them do have AD.
13 And that entire question ended up being
14 narrowed down to one voting question initially, which
15 was possible or probable AD, which of course is the
16 group that you would least expect to benefit from
17 PET, because they already have gone through the two
18 to three years of making that, that typically occurs
19 to make that diagnosis accurately, and time has
20 already elapsed that we are trying to save.
21 And so then at that point, and Dr.
22 Papatheofanis alluded to this, Dr. Tunis essentially
23 said wait a minute, guys, what about this whole group
24 of mild cognitive impairment patients that you were
25 charged to look at and you haven't even voted on
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1 them. And then a second motion was made to vote on
2 mild cognitive impairment which, by taking it apart
3 in this was, was led to say well, we don't have
4 enough evidence in treating mild cognitive impairment
5 that is useful, and so we'll dispense with that.
6 And what they still haven't voted upon was
7 the patients who don't meet mild cognitive impairment
8 definition, like the age associated impairment, and
9 most importantly, the patients who are demented but
10 are thought to have possible or probable AD, and a
11 number of them actually do. Which means that if you
12 treated patients according to the diagnosis, they
13 would fail to get the treatment that everyone here
14 agrees could benefit those patients tremendously.
15 DR. SOX: Okay. I think it's time to move
16 on. Thank you very much, Dr. Silverman, and we will

17 now hear from Dr. Peter Conti. Would you please
18 introduce yourself, state any conflicts that you may
19 have.
20 DR. CONTI: Good morning, Mr. Chairman and
21 members of the panel, ladies and gentlemen. My name
22 is Peter Conti. I am associate professor of
23 radiology at the University of Southern California.
24 As far as conflicts are concerned, I have a number of
25 consulting opportunities for equipment manufacturers
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1 and service providers for PET radiotracers and PET
2 procedures. I am also funded by several government
3 agencies to conduct research in the field of PET, but
4 I am now speaking on behalf of the Society of Nuclear
5 Medicine.
6 I would like to offer our strong support
7 to the addition of AD as a CMS reimbursable
8 indication for FDG PET. We would like to reiterate
9 our position presented to the diagnostic imaging
10 panel on January 20th, 2002.
11 Right now more than 19 million Americans
12 are estimated to be caring for someone with AD, and
13 home care for a person whose disease has progressed
14 is estimated to cost about $47,000 per year. By the
15 middle of the next century, as many as 14 million of
16 today's baby boomers could have AD. As you know, the
17 standard wisdom is that there is no definitive way to
18 diagnose AD other than by brain biopsy or autopsy.
19 The information compiled by the UCLA group
20 and presented to CMS from studies all over the United
21 States strongly supports the value of PET as an
22 alternative diagnostic approach for this devastating
23 condition. You will hear in a few moments additional
24 material from the University of Michigan which will
25 be presented by Dr. Kirk Frey, independently
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1 supporting these conclusions.
2 We believe that there are compelling
3 reasons why PET is a valuable tool for physicians
4 attempting to determine whether the memory lapses and
5 behavior patterns seen in these patients are due to
6 Alzheimer's disease or to some other process. Number
7 one, since FDG PET is more effective than clinical

8 examination for the differential diagnosis and
9 identification of various dementia causes, the
10 greater diagnostic accuracy provided by PET early in
11 the course of dementia illness will lead to more
12 effective disease management.
13 PET enables physicians to clearly identify
14 and differentiate between different types of
15 dementia. This can be critical, not only for the
16 treatment of these other diseases, but for the
17 initiation of Alzheimer's specific medication.
18 Third, notwithstanding the potential for
19 therapeutic intervention, the usefulness of FDG PET
20 is important for patient quality of life.
21 Specifically, additional certainty with respect to
22 the diagnosis will help the patient and family make
23 more appropriate life decisions. In addition, the
24 increased certainty may help family members cope with
25 the condition; for example, depression affects more
.00061
1 than half of primary family caregivers and
2 uncertainty about the diagnosis may contribute to
3 family and caregiver feelings of depression and
4 helplessness. A negative study would be of value to
5 patients as well, as it can predict the absence of
6 further cognitive impairment with fairly high
7 certainty, which could well affect the decisions the
8 patient and family make about the future, such as
9 retirement, moving or staying near home, not taking a
10 cholinesterase inhibitor, et cetera.
11 In short, the radiopharmaceutical FDG with
12 PET can be used to assist with the characterization
13 of early dementia in geriatric patients for whom the
14 differential diagnosis includes one or more kinds of
15 neurodegenerative disease associated with the
16 dementia process.
17 We believe in particular, this is
18 particularly helpful in this patient population when
19 there has been a change in cognitive status where the
20 etiology is not apparent or when symptoms are not
21 reversed in a reasonable amount of time. Providing
22 families and physicians with the means to better
23 manage those with this disease would seem a more cost
24 effective approach to care. We believe this approach

25 should include access to and reimbursement for PET
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1 scans.
2 We disagree with the conclusions and
3 recommendations offered by the Diagnostic Imaging
4 Panel on January 20th, 2002. The reasons for this
5 disagreement include the following: Number one, the
6 analysis performed by the outside Duke University
7 team corroborated the fact that PET is in fact more
8 accurate compared to standard methods of detection of
9 AD; perhaps that's an area of agreement rather than
10 disagreement. Two, the analysis that includes the
11 treat-all strategy used by the Duke team has no
12 precedent, at least none that was offered to the
13 community during the debate; this potentially limits
14 the usefulness of the results obtained.
15 A more traditional approach such as
16 looking at equivalents or superiority to the existing
17 methods should have been applied. In fact, time does
18 not permit me to list the numbers of procedures that
19 are done in practice today which are covered by CMS
20 that do not affect the outcome of patients, or
21 diseases that have no treatment.
22 There was no accounting, third, of the
23 extra burdens that's placed on physicians and
24 patients in determining who should be treated and
25 when. The treat-all strategy is not practical from
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1 cost, drug interaction and time to delay diagnosis
2 perspectives. Elderly patients taking multiple drugs
3 for other disorders with limited budgets cannot be
4 expected to comply. Clearly, more accurately
5 identifying patients with disease would lead to a
6 more informed decision as to whether to treat such a
7 vulnerable population. In fact, it would likely be a
8 requirement for CMS, given the latest information
9 from the White House to develop appropriate
10 diagnostic strategies for identifying patients that
11 have this disease.
12 Fourth, therapeutic options will change
13 over time. Any policy decision should have the
14 flexibility to withstand the flow of changes in
15 healthcare, especially treatment options. A serious

16 problem has now been introduced regarding treatment
17 development for these patients. From the data
18 presented by the Duke team a large position of
19 patients may be misdiagnosed with AD if traditional
20 diagnostic methods continue to be employed.
21 This means that because the entrance
22 criteria for investigator or drug company sponsored
23 trials will permit a large mixed patient population,
24 results will be significantly biased. Certainly
25 tightening the criteria used by using PET, which they
.00064
1 admit improve diagnostic accuracy, is more
2 appropriate.
3 We therefore urge you to reject the
4 conclusions reached by the Diagnostic Imaging Panel
5 and add AD to the list of reimbursable indications.
6 In the event you consider approving the indication,
7 we have provided written language available for use
8 in formulating the indication, and I will just read
9 that very briefly.
10 This is the proposed language for use of
11 FDG PET in dementia. An adjunct test to assist the
12 diagnosis of early dementia in geriatric patients for
13 whom the differential diagnosis includes one or more
14 kinds of neurodegenerative disease; for example, AD,
15 and frontal temporal dementia. The criteria for
16 appropriate use of PET FDG in the evaluation of
17 dementia should include, one, presentation of
18 cognitive impairment or behavioral problems
19 representing a change from the patient's normal level
20 of functioning. Two, the etiology of symptoms not
21 apparent or symptoms not reversed with reasonable
22 amount of time following initial evaluation and
23 management emanating from standard workup. And
24 third, patient is not suffering from a state of
25 advanced dementia at the time the PET scan is
.00065
1 acquired.
2 I would now like to take the opportunity,
3 if there are no questions, to introduce Dr. Kirk
4 Frey, from the University of Michigan. He is the
5 president of the Brain Imaging Council of the Society
6 of Nuclear Medicine. I will take some questions

7 before Dr. Frey does take the podium.
8 DR. SOX: Questions of clarification for
9 Dr. Conti? Any questions from the panel? In that
10 case, proceed.
11 DR. FREY: Thank you for the opportunity
12 to address the committee this morning. I'm Kirk
13 Frey, from the University of Michigan. I am a
14 professor in the Departments of Neurology and
15 Radiology, and I come to you wearing two hats, one as
16 an investigator involved in designing and applying
17 tests of brain chemistry and function, particularly
18 with an interest in neurodegenerative disorders like
19 Alzheimer's and Parkinson's diseases and second as a
20 practicing neurologist in a geriatric referral clinic
21 where patients with these kinds of problems present
22 for evaluation.
23 Let me share with you briefly some data
24 from our laboratories that were not available to the
25 committee for review because they had been abstracted
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1 but not yet formally published in the reviewed
2 medical literature. These support the conclusion
3 regarding the diagnostic impact and accuracy of PET
4 in the evaluation of patients with suspected AD but
5 they come from an unselected clinical population
6 recruited in our university.
7 This study was a prospective design. We
8 went to our clinics and enrolled patients who were
9 presenting at their initial visit for a newly
10 discovered cognitive complaint or abnormality. We
11 included two clinics to select these patients, one a
12 specialty clinic in geriatric neurology where I
13 practice, and the second was a general neurology
14 clinic at our adjacent Veteran's Hospital, which is
15 more representative of primary contact general
16 neurology.
17 All patients underwent a standardized
18 clinical evaluation as recommended by the AAN for
19 evaluation of suspected dementia. We then employed a
20 two-year follow-up period to establish an operational
21 clinical diagnosis. And we distinguished patients
22 into groups of progression of their cognitive
23 complaint versus no progression. At the entry into

24 this study we performed an FDG PET scan, but this was
25 not utilized in formulating the patient's clinical
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1 diagnosis.
2 We analyzed this PET scan objectively
3 according to the presence or absence of a pattern,
4 which I loosely refer to here as the AD pattern.
5 This was done with an objective tool to look at the
6 metabolic deficit in association cortical areas
7 relative to primary sensory motor cord disease.
8 This cartoon shows the pattern of FDG that
9 we used. I won't spend your time here other than to
10 say there are a number of recognized patterns and we
11 combined all of those that are associated with
12 degenerative dementias into those we considered
13 positive. Yes.
14 DR. FRANCIS: Were the results of the PET
15 scan known to the people doing the clinical
16 evaluation?
17 DR. FREY: No, they were not, and in terms
18 of making the clinical distinction here, we
19 abstracted from the patient's chart the objective
20 neurological findings rather than looking at the
21 treating physician's clinical diagnosis.
22 So we enrolled 116 patients. Of these, 90
23 completed their two-year clinical follow-up. There
24 were 26 where incomplete data were available to us,
25 and to look at whether those might have influenced
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1 the result due to dropout, we found that of those 26
2 patients that didn't complete the follow-up, 10 were
3 felt to be not initially demented on the basis of
4 neuropsychometric and clinical testing; 15 were
5 demented on that initial exam.
6 And let's look at those. If we took the
7 PET data from those 26 patients, those who were not
8 initially demented all had a PET pattern which did
9 not indicate the presence of AD. 9 of the 16 who
10 were demented on their initial examination did have a
11 positive AD pattern. And the reasons for withdrawal
12 are listed here on the right. Largely these were
13 patients who came from a distance to our medical
14 center; many died without autopsy or were unable to

15 be located for follow-up.
16 With regard to the patients who did
17 complete, these are the findings. The numbers here
18 reflect the fraction of PET scans that were
19 interpreted by our objective estimator as positive
20 for the AD pattern and you see first amongst those
21 with a progressive cognitive decline over two years,
22 we had an 80 percent sensitivity.
23 We found 7 of 31 patients had an AD like
24 pattern but did not have a progressive dementia. It
25 turns out that these represented two areas of false
.00069
1 positivity. First, there were patients who had
2 relatively advanced multiple sclerosis. This was
3 evident to the referring physician on the basis of
4 magnetic resonance imaging but this was not available
5 to us in terms of interpreting the PET data. So this
6 was done in an isolated and blinded fashion.
7 The other patients in this group suffered
8 from alcohol and polysubstance abuse. When one
9 looked at the fraction of patients who actually
10 satisfied after two years the clinical research
11 diagnostic criteria for probable or definite AD and
12 compare those against patients who ultimately were
13 neurologically normal, that is, these are patients
14 with an unsubstantiated complaint or who had
15 depression or other psychological problem which
16 resolved, we found that the sensitivity of the FDG
17 PET was 89 percent and the specificity 100 percent.
18 Overall, the diagnostic accuracy here was
19 90 percent and data agree very favorably with the
20 data that the diagnostic panel had for review, but
21 this now is an unbiased prospectively defined
22 clinical population, which is exactly the situation
23 where we would argue the diagnostic impact of PET
24 might best be identified.
25 So as I have already told you, we found
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1 some false positives. For the most part, these would
2 have been clinically evident by combining the PET
3 data with the routine clinical information collected
4 by the neurologists at the time. False negative
5 studies, I should point out that none of the patients

6 who progressed actually had a completely normal FDG
7 scan. Instead, they had patterns that we were not
8 willing to call diagnostically positive, and it turns
9 out that as a result of this, and let me just skip
10 forward, we actually identified that we could
11 increase the sensitivity. That is, if we looked at
12 the patients who had mild cognitive impairment at the
13 time of entry, rather than limiting ourselves to the
14 neocortical changes here in the parietal lobe and
15 here in the frontal lobe, which were our a priori
16 assumptions of areas to look at, it turns out that
17 the posterior singular cortex is actually the most
18 sensitive area to look for very early changes in
19 dementia, and all of these cases that we identified
20 as negative who later progressed showed a decrease in
21 this posterior singular region.
22 So, if we were to modify further our
23 objective criteria as to how to interpret FDG, we
24 think that its performance would be even better than
25 what we reported here.
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1 Let me now change hats from that of the
2 imaging scientist to the clinician in the geriatric
3 neurology clinic dealing on a daily basis with
4 patients who come with a new complaint. Patients
5 come to us expecting two results; they come to us
6 with hopes and with expectations. They hope that the
7 problem they come to us to evaluate is something
8 where we can have a positive impact and resolve for
9 them, but they expect to receive an accurate
10 diagnosis and an accurate prognosis as to what the
11 future holds for them and what the medical
12 explanation for their complaint is.
13 The assessment done by the Duke EPC, I
14 think addresses the issue of patient hope very
15 nicely. Given the somewhat limited impact of
16 available treatment for AD at the present time, it
17 can be concluded based on the data manipulations that
18 were made that the treat-all strategy is somewhat
19 better than the treat-none strategy, and because the
20 impact is relatively difficult to demonstrate,
21 particularly with more advanced Alzheimer's cases,
22 the change in terms of life expectancy or quality of

23 life may not be a large measure.
24 On the other hand, the impact of actually
25 making an accurate and correct medical diagnosis when
.00072
1 a patient presents with a complaint is not at all
2 weighted in the Duke analysis. In fact, what we see
3 in our clinics in Ann Arbor is a very large portion
4 of patients who have come from an initial evaluation
5 where a diagnosis was not made an a medication was
6 started. The patient then fails to achieve what they
7 expect in terms of medical benefit and it referred on
8 to yet another evaluation by another specialist.
9 This is a very frustrating situation for the patient.
10 It's a very frustrating situation for the referring
11 or for the consultant physician as well, to tell the
12 patient that they may or may not have received an
13 adequate diagnostic evaluation, and that you may or
14 may not be able to answer the question as to what the
15 underlying cause for the complaint might be.
16 So I would encourage you to consider the
17 value of diagnosis in a patient with a complaint that
18 may or may not represent the early signs of AD as an
19 important and unweighted value in your assessment so
20 far. Thank you.
21 DR. SOX: Thank you. Are there any
22 questions, clarifications for Dr. Frey? Yes, Randel?
23 MS. RICHNER: You said that this
24 information was in abstract form. I'm not sure, were
25 you aware that the Duke EPC study was going on in
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1 evaluating this, and were you given the opportunity
2 to provide this information to Duke?
3 DR. FREY: No. I became aware of it at
4 its publication on the Internet in December.
5 MS. RICHNER: Okay. Because one of the
6 things that we talked about as an executive committee
7 a few years ago was that we would use unpublished
8 data for evaluations of technology assessment, and I
9 remember that discussion well with Dr. Brook and
10 others. So I think that this to me is very
11 compelling information that wasn't necessarily
12 considered in this evaluation, and that should be
13 part of the process. Once again, we're still having

14 problems with process. The questions again is an
15 issue and then now this, getting data after the fact
16 that was this very very interesting data. So I think
17 as a point on the record, I know that this afternoon
18 we're going to be talking again about process issues
19 with the EC, but once again, we need to clarify what
20 we're doing when and how and what kind of data we are
21 going to be using in our evaluations. And also, the
22 questions, again.
23 DR. FREY: But I would point out that your
24 analysis of the published literature led to largely
25 the same conclusions about the diagnostic performance
.00074
1 of this test.
2 DR. McNEIL: Actually that was my point,
3 Randel. I think we as a group wanted to get all of
4 the data that we can, and in this particular case,
5 nice as that study is, it doesn't impact at all on
6 the data that we used in the Duke analysis, and it
7 essentially comes down to the same point. But it
8 does raise the issue which we should discuss later
9 about abstract data, and how much we include and
10 where we get it, but I don't think that's relevant
11 for the process issues here. I think it's a little
12 bit of a red herring at this point.
13 DR. SOX: There will be plenty of time for
14 this sort of discussion when we get after the break,
15 so let's try to stick with questions for Dr. Frey.
16 Frank.
17 DR. PAPATHEOFANIS: You described in your
18 study at Ann Arbor that you obtained a baseline PET
19 and then tracked the patients for two years with a
20 clinical correlation there. Were any other
21 noninvasive studies performed at baseline, like MR or
22 HMP or SPECT?
23 DR. FREY: Yes. We performed a
24 stereotypic evaluation based on the then current AAN
25 guidelines, which included either a CTR and MR,
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1 depending on whether the patient had already received
2 neuroimaging or not, a battery of blood testing and
3 neuropsychometric testing to document complaints that
4 weren't objectively obvious on bedside confrontation

5 or neurologic exam.
6 DR. PAPATHEOFANIS: Were you able to
7 evaluate their predictive strength, if you will, the
8 MR and so forth, two years down the line?
9 DR. FREY: We could do that, I have not
10 looked at it, but suffice it to say that the vast
11 majority of these were negative, other than for the
12 presence of additional medical conditions such as
13 demyelinating disease in 5 of the 7 false positive
14 studies.
15 DR. SOX: Bob.
16 DR. BROOK: If I heard your testimony
17 correctly, you seem to agree with everything except
18 the point of the accuracy of the diagnosis, in terms
19 of giving patients better information.
20 DR. FREY: Yes, but I think that --
21 DR. BROOK: I mean, the treat-all versus
22 -- I mean, you concluded by saying the only real
23 issue is that Duke didn't consider the expectation
24 that the patients have, the multiple visits and all
25 that kind of stuff.
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1 DR. FREY: And I consider that to be an
2 absolutely insurmountable shortcoming.
3 DR. BROOK: I understand that, but given
4 what you know about sensitivity and specificity, and
5 what you heard, how would you change your message
6 when you have somebody who presents with dementia and
7 you have diagnosed this as -- you have done the
8 memory tests, you know that this thing only has a
9 sensitivity of .9, what do you tell the patient
10 differently after you do the PET than before you did
11 the PET?
12 DR. FREY: So the impact here would be --
13 DR. BROOK: I'm asking you as a clinician,
14 I'm coming to you and I just couldn't understand the
15 logic between the two parts of your testimony.
16 DR. FREY: The example would be a patient
17 who has a memory complaint, who comes --
18 DR. BROOK: Yes. I mean, that's
19 presumably who you're evaluating, has a memory
20 complaint, you did everything possible, you don't
21 know exactly what's going on, you're the best

22 clinician in the state of Michigan, and you now do a
23 PET that has a sensitivity of .9, it turns out to be
24 normal. Do you really tell me that you know any more
25 than what you knew now? Because you're already up at
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1 a level of this curve, and I just don't understand
2 your testimony.
3 DR. FREY: The critical missing value here
4 is that it takes two years of prospective follow-up
5 in order to properly categorize the patient, whereas
6 at the time they initially present to me, if I have
7 the neuroimaging data from PET, I can achieve
8 virtually an equivalent diagnostic specificity and
9 specificity as if I follow the patient in the clinic
10 telling them I don't know what you have, come back in
11 six months, we'll see if you're worse.
12 The analogy to this would be to turn the
13 clock back about 20 years in the diagnosis of
14 multiple sclerosis, where patients would shop from
15 physician to physician to physician with a complaint
16 that we would all objectively find on neurologic
17 examination but not be able to make the diagnosis
18 of --
19 DR. BROOK: So you're --
20 DR. FREY: -- demyelinating disease.
21 DR. SOX: Don't interrupt, Bob. Give him
22 a chance.
23 DR. BROOK: I don't understand. You're
24 using it in a positive way.
25 DR. FREY: Yes.
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1 DR. BROOK: You're saying that at baseline
2 you don't know the diagnosis, and if it's positive,
3 you are going to tell the patient that basically they
4 have AD, is that how you're using it?
5 DR. FREY: I would use it in both ways, so
6 that if you come to me at a time I cannot objectively
7 show that you have a progressive dementia, that you
8 have a complaint that fits in the Alzheimer's sphere,
9 if I have this additional side data and your scan is
10 unequivocally abnormal, I would tell you so and we
11 would manage your case expectantly, as though you
12 have early incipient AD and you should have available

13 to you all of the healthcare resources that you have
14 heard may have an impact, and particularly a greater
15 impact when applied earlier in the course.
16 Conversely, if your scan was absolutely
17 normal, together with the other clinical information
18 I have, I would counsel you that we do not find
19 evidence that projects that you are going to
20 experience a significant decline in your cognitive
21 abilities over the next several years, and we should
22 work behaviorally to try to maximize your abilities,
23 to treat your depression, your anxiety and so on, and
24 not assign you the diagnosis of probable AD and do
25 you and your family the disservice of assuming that
.00079
1 you're going to have short-term further loss of
2 abilities that are medically managed with
3 cholinesterase therapy.
4 DR. BROOK: May I ask one follow-up
5 question?
6 DR. SOX: Yes.
7 DR. BROOK: I'm still confused, and I'm
8 really sorry. You have done a really superb workup
9 and you're a superb doctor. And you can't tell
10 whether this is progressive, that's what you're
11 telling me?
12 DR. FREY: And that's true when you see
13 the patient for the first time 90 percent of the
14 time.
15 DR. BROOK: Absolutely. And the PET scan
16 in that situation turned out to be normal. Would you
17 not treat the patient?
18 DR. FREY: I would not treat the patient
19 expectantly with a cholinesterase inhibitor, who's
20 shown not --
21 DR. BROOK: Would you treat the patient
22 with a cholinesterase inhibitor?
23 DR. FREY: No, I would not.
24 DR. BROOK: So you would use the PET scan
25 and all you know about sensitivity and specificity,
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1 and the Duke analysis, and you as a clinician would
2 not treat any patient whose PET scan was not
3 definitively abnormal in the absence of cognitive

4 decline, a history and physical exam cognitive
5 decline. Is that what you're testifying, and that's
6 how you think it's valuable to you as a clinician?
7 DR. FREY: I would qualify a little bit,
8 and I would say this is in a setting where I am not
9 able to make a definite clinical diagnosis, that's
10 correct. I think this is valuable side information
11 with independent impact.
12 DR. BROOK: And of all the patients that
13 you see, what proportion of them fall into that group
14 at the first visit?
15 DR. FREY: It's difficult to get an
16 accurate estimate, but I would say between 1 in 10
17 and 1 in 5.
18 DR. BROOK: So for 1/20 to 1/10 of all of
19 the patients you see, you would not start them, who
20 had problems with memory, but you can't deal with
21 memory change over time, they clearly are there and
22 they have some memory impairment.
23 DR. FREY: No. They have a memory
24 complaint. I mean, here is the difficulty. The
25 objective tools we have for clinically evaluating
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1 patients are relatively crude until the deficit is
2 self evidently obvious to all in the family and
3 everyone around. Patients are introspectively very
4 much more sensitive to the presence of a change from
5 their baseline than many of us in the office are able
6 to substantiate. Most of us, at least in our clinic,
7 do not intervene with the treatment which is
8 established for AD until we are able to make a
9 clinically defensible diagnosis that indeed we think
10 the patient has AD.
11 DR. BROOK: I would just add one little
12 comment. As an internist and geriatrician, if I take
13 a sensitive enough history, I can get anybody over
14 the age of 65 to indicate that they have a memory
15 complaint compared to when they were 20, and if I
16 follow your logic correctly, what you're recommending
17 is everyone ought to get a PET scan that I as a
18 primary care internist -- you didn't, you know, if I
19 follow you correctly, that I as a primary internist
20 ought to give every person literally that comes in

21 and says I have a memory complaint, because I surely
22 can't, even if I send them to you or make a diagnosis
23 of dementia on this group because they don't have any
24 positive testing. And the bottom line is, every one
25 of those people deserve a PET scan.

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1 DR. FREY: Well, remember, these are
2 patients that were referred for a neurological
3 consultation to evaluate the problem, so it must
4 have --
5 MS. RICHNER: They had already been
6 through it.
7 DR. SOX: Bob, are you done?
8 DR. BROOK: I'm finished.
9 DR. SOX: Thank you. John?
10 DR. FERGUSON: Were all the PET scans read
11 blindly so those who read them and interpreted the
12 PET scans did not know the clinical course?
13 DR. FREY: That's correct. They knew that
14 it was part of this study so that the patient had a
15 cognitive complaint or concern, but they did not have
16 access to any other clinical data at the time of the
17 PET analysis, that's correct.
18 DR. FERGUSON: And were there follow-up
19 PET scans besides the initial one?
20 DR. FREY: There were not unless the
21 patient elected to enter a research protocol that
22 might have entailed additional imaging.
23 DR. SOX: Thank you very much, Dr. Frey.
24 We will now hear from Dr. Marilyn Albert, from
25 Massachusetts General Hospital. Could you provide

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1 any further introduction that suits you and tell us
2 about any conflicts.
3 DR. ALBERT: My name is Marilyn Albert and
4 I am professor of psychiatry and neurology at the
5 Harvard Medical School. I am also the director of
6 the gerontology research unit at Massachusetts
7 General Hospital and I am co-director of a clinic,
8 the geriatric neuro-behavioral clinic at
9 Massachusetts General Hospital, where we see patients
10 with cognitive decline. But, I'm speaking to you
11 today in my position as the chair of the medical and

12 scientific advisory committee of the Alzheimer's
13 Association, and I am here just to present the
14 position of the Alzheimer's Association with respect
15 to the issue that's before you this morning. I have
16 no conflicts.
17 The Alzheimer's Association, as you
18 probably know, is next after the Federal Government,
19 the largest funder of research in the field of Ad,
20 but it also carries out many other important
21 activities, including trying to provide support and
22 family care to patients, trying to provide
23 information. And in the scientific domain, one of
24 the things that it sponsors is working groups among
25 scientists in the area that are a continuing activity
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1 of communication among scientists and we have working
2 groups related to diagnostic imaging. And we have
3 working groups related to diagnosis per se, and the
4 position of the Alzheimer's Association that I bring
5 to you this morning comes from the activity of those
6 working groups that have considered what the current
7 status is of diagnosis, and what the current status
8 is about imaging in relationship to diagnosis.
9 The general consensus of the members of
10 these working groups is that the clinical diagnosis
11 as it is currently used is the current state of the
12 art and that while PET scanning and other forms of
13 imaging modalities are extremely important
14 potentially for diagnosis and for monitoring disease
15 and evaluating the potential impact of medications,
16 that right now they are at the experimental level and
17 are, there is insufficient evidence to suggest that
18 they should be substituted for the standard clinical
19 diagnostic workup. That's really the basic position
20 of the association and I would be happy to answer any
21 questions you might have about that or anything else.
22 DR. SOX: Perhaps you could respond to
23 this issue about treating patients with
24 cholinesterase inhibitors when you have a 20 or 30
25 percent probability that the patient has a condition
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1 that would respond to that drug, whether it would be
2 appropriate to treat those patients.

3 DR. ALBERT: You're talking about very
4 very mild patients, or anybody at any stage who has a
5 possibility of having a disease?
6 DR. SOX: Patients like those in the
7 trial.
8 DR. ALBERT: I was obviously correctly
9 quoted this morning as saying that I think that
10 anybody, if we could identify people accurately who
11 have early disease, there would be enormous benefit.
12 Myself and many other people around the country are
13 doing a lot of research in specifically that area.
14 That happens to be my own scientific area of
15 interest, to find out how to identify people as early
16 as possible in the course. The motivation for that
17 work is that we believe that in the future there will
18 be more effective treatments than there are now, and
19 it's likely that they will have negative side
20 effects, many more negative side effects than current
21 treatments currently provide, and at that point it
22 will be really essential to identify people as early
23 as possible.
24 Currently the way that patients are
25 treated in my clinic and in clinics around the
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1 country as best I know, is that not only patients who
2 meet the criteria for probable or possible AD are
3 treated, but some patients who meet criteria for
4 so-called MCI or mild cognitive impairment who don't
5 yet meet the clinical criteria for dementia are also
6 treated. The reason that's the case is that as you
7 have heard, the downside of treating them is minimal
8 and the upside is possible, although it hasn't been
9 proven.
10 DR. SOX: So it sounds as though you don't
11 have a quarrel with the analytic strategy that the
12 Duke group took.
13 DR. ALBERT: No, I don't.
14 DR. SOX: Wade.
15 DR. AUBRY: I just had a question
16 regarding the language. In your statement, you said
17 substituted for a clinical evaluation. Is that what
18 you meant to say, or did you mean an adjunct, or to
19 assisting the diagnosis?

20 DR. ALBERT: The position of the
21 association is that are certainly a subset of cases
22 where doing PET scanning will improve the diagnosis
23 but as I understand the question before the
24 committee, that's not the question being addressed.
25 DR. SOX: Other questions for Dr. Albert?
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1 Don't go away. Leslie, did you have a question?
2 DR. FRANCIS: I guess I would like to ask
3 you whether you agree with what some of the other
4 people said. I think you did, about the downside of
5 the treat-all strategy, that is, the Duke model
6 assumed that there is very little downside. Do you
7 agree with that, or with the people that argue there
8 is more of a downside, and do you manage differently
9 patients who you start on therapy and they do show
10 some side effects, would PET be useful in that group?
11 DR. ALBERT: With response to the second
12 question, to my knowledge, there are no data that PET
13 can identify patients who might particularly benefit
14 from treatment, so I can tell you what's happening in
15 clinical practice and certainly in our clinical
16 practice is that we are more and more likely to treat
17 people at mild or in milder stages. In our research
18 study we have people who meet criteria for so-called
19 MCI who are not yet clinically demented, and we feel
20 sufficiently strongly that even though there is no
21 proof yet that these medications are helpful that we
22 ought to offer them and present them to people as a
23 possible intervention.
24 So we provide it, and the reason that we
25 provide it if people are interested is because it's
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1 not likely to make them ill and it has the
2 possibility of benefit, but we would certainly not do
3 that if we thought that people could become acutely
4 ill, so we would completely reevaluate the strategy
5 if we had medications that had a larger downside. So
6 I think we act in accordance with the model that the
7 Duke group developed.
8 DR. SOX: Bob.
9 DR. BROOK: I would like to ask the
10 clinical question again. The recommendations and the

11 process is sort of everybody, and are there any
12 subgroups that you can think of given what you know
13 about the sensitivity and specificity of PET, that
14 this test would add something to the clinical care of
15 those people, either the group that Leslie talked
16 about, which was people that developed side effects
17 and you want to know whether to push it over the side
18 effects, or other diseases for which these drugs may
19 interact with, or anything else. Is there any single
20 subgroup that the Alzheimer's Association has looked
21 at that believes that this thing should be standard
22 practice, not overall, but a clinical subgroup?
23 DR. ALBERT: I don't believe that the
24 Alzheimer's Association has identified a subgroup
25 where they think this approach would be beneficial.
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1 I can tell you from my own personal opinion
2 clinically that if I have a patient who I think might
3 have frontal temporal dementia, I would be very
4 likely to try to do some functional imaging study,
5 either PET or SPECT, but that's not the position of
6 the Alzheimer's Association.
7 DR. BROOK: And why do you do this and how
8 do you use it? I mean in sort of the model, the
9 process that the committee used, what's the value of
10 it in this patient?
11 DR. ALBERT: There is some evidence that
12 patients with frontal temporal dementia are very
13 likely to have frontal hypoperfusion or more
14 unilateral hypoperfusion than is typical in the
15 average Alzheimer case. And so, if we suspect
16 frontal temporal dementia, and the clinical case is
17 very confusing, then we might be likely to do a
18 functional imaging scan. But as you were suggesting,
19 certainly in our clinical practice we put a great
20 deal of emphasis on getting a good history, and the
21 best way of identifying frontal temporal dementia is
22 still a good clinical history.
23 MS. RICHNER: I think the question again
24 is, if you do the PET scan, will there be any change
25 whatsoever in terms of how you treat the patients,
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1 because you really don't have a lot of choices in how

2 it would be treated; is that right?
3 DR. ALBERT: We don't typically do PET
4 scans as part of our workup.
5 MS. RICHNER: But in those cases where you
6 say you would use a PET scan, would there be any
7 change in the treatment?
8 DR. ALBERT: I actually don't think so,
9 and part of the problem is that we don't have good
10 treatments for frontal temporal dementia.
11 MS. RICHNER: Right, so there's no change.
12 DR. ALBERT: And it's possible that the
13 cholinesterase inhibitors might help them, we don't
14 know, so it wouldn't change treatment.
15 MS. RICHNER: I see, thank you.
16 DR. SOX: Tom.
17 DR. HOLOHAN: Let me just clarify what you
18 said, which is not what's being repeated. You said
19 PET or SPECT, did you not?
20 DR. ALBERT: Yes.
21 DR. SOX: Any other questions? Thank you
22 very much. Now, we are running a bit behind but I'm
23 going to press on before the break with open public
24 comments, and I would like anybody who is interested
25 in making comment during the 15 minutes that we have
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1 allotted to this to raise their hands. One person,
2 two people. Well, I'm not going to give you seven
3 minutes each. Three minutes. So why don't you who
4 put your hand up first, go ahead. Introduce
5 yourself, tell us about any conflicts, and then go
6 ahead.
7 DR. JOHNSON: My name is Keith Johnson. I
8 am a neurologist at Brigham and Women's Hospital and
9 Massachusetts General Hospital in Boston. I have
10 specialized in the diagnosis and management of AD for
11 about 15 years. I am also engaged in research and
12 the practice of nuclear medicine, and I have no
13 conflicts.
14 I would like to raise a couple of points
15 that may represent benefits for the use of PET in the
16 diagnosis of AD that may not have been adequately
17 considered. The first is the length of time required
18 to arrive at a confident diagnosis of AD or dementia,

19 or MCI. The second point is the value of knowing the
20 diagnosis for patients and their families.
21 First, many elderly patients present with
22 a clear history of progressive cognition and
23 functional decline. They satisfy criteria for AD and
24 are begun on a cholinesterase inhibitor. However,
25 for a substantial number of patients and an
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1 increasing number who are in the early stages of
2 impairment, there is a significant time lag between
3 an initial evaluation of memory trouble and a
4 confident diagnosis followed by appropriate
5 treatment. This is true primarily because the
6 diagnosis is to a large extent focused on proving
7 that there has been progressive deterioration, i.e.,
8 observed decline in cognition and function over a
9 period of six months to one year or more.
10 This specific limitation of the clinical
11 evaluation would in many cases be significantly
12 reduced with the use of PET, because diagnostic
13 accuracy would be increased at an earlier stage of
14 the illness, permitting earlier initiation of drug
15 therapy. And we now have evidence, as you've heard,
16 that the benefit of cholinesterase therapy is reduced
17 when the initiation of treatment is delayed until
18 later in the course of AD. We also recognize that a
19 less certain diagnosis is very often associated with
20 over utilization of medical resources by individuals
21 who are fearful of the diagnosis.
22 The majority of dementia patients are
23 evaluated not by specialists who are skilled in the
24 diagnosis of AD, but rather by busy primary care or
25 internal medicine physicians for whom an efficient
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1 and accurate diagnostic aid would be particularly
2 beneficial.
3 Secondly, it is often the case in my
4 clinical experience that major life decisions are
5 initiated on the basis of a diagnosis of AD,
6 including changes in place of residence, property
7 ownership, financial planning and employment.
8 Patients and their families need to anticipate future
9 healthcare needs, changing requirements for mobility

10 and transportation, as well as safety measures.
11 Individuals who may be more confidently given a
12 diagnosis of AD and those who are reassured by a
13 negative PET scan may both derive direct benefits
14 from a test that will significantly enhance the
15 certainty of the diagnosis.
16 DR. SOX: Thank you. Any brief questions
17 for Dr. Johnson? Thank you very much, sir. The next
18 speaker, please introduce yourself and --
19 DR. SMALL: Yes. I'm Dr. Gary Small and
20 you heard about my conflicts earlier and my titles
21 and so forth.
22 I just want to, I appreciate having
23 another opportunity to come up and make a few other
24 points after hearing the other comments, and I would
25 reiterate that it does, it takes us several years to
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1 arrive at an accurate diagnosis without the use of
2 PET and by using conventional methods, and this is
3 pretty typical around the country.
4 I was interested in hearing Dr. Albert's
5 experience at Harvard and Mass General, and my own
6 experience at UCLA and also in talking with leaders
7 around the country, other centers, that this is
8 actually not going on, that most experts I've talked
9 to are not routinely treating MCI with cholinesterase
10 inhibitors. In fact, right now there are clinical
11 trials of cholinesterase inhibitors, comparing them
12 to placebo in this group, so we are still waiting to
13 see what the outcome of those treatments are going to
14 be. So that in my own experience and talking with
15 leaders around the country, that's not the case.
16 And I showed some of the data in terms of
17 whether in primary care, this is actually being done
18 or recognized and in fact in the real world with the
19 primary care physicians, the dementia patients are
20 not even being treated, let alone the MCI patients
21 being treated and diagnosed. So, I just wanted to
22 make those few points.
23 DR. SOX: Thank you very much. Follow-up
24 questions? Yes, Sean.
25 DR. TUNIS: Just to take an opportunity.
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1 You're actually a member of the practice parameters
2 committee for the American Academy of Neurology
3 guideline that's been mentioned a fair bit today; is
4 that correct?
5 DR. SMALL: That's correct.
6 DR. TUNIS: So, I'm just wondering if you
7 can kind of update us. I'm assuming that you all
8 have been in touch with the folks on that committee
9 and the chair of that committee to talk about the
10 relationship of their nonrecommendation for PET in
11 and the evaluation of suspected dementia. I'm just
12 wondering, can you update us on where the Academy is
13 regarding this?
14 DR. SMALL: Yes, and thanks for asking
15 about that. As it turns out, the Academy at the time
16 that we made on our recommendations, the issue of
17 data that was available was relevant, because the
18 paper that has been referred to several time,
19 Silverman, et al., showing the high sensitivity and
20 specificity of PET, had not been accepted for
21 publication, so that wasn't considered during those
22 deliberations. The committee has not formally met
23 recently.
24 However, Dr. Jeff Cummings and I, along
25 with another American Academy of Neurology leader,
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1 Dr. Meader, wrote a letter to the committee making
2 many of the points that I have made today about the
3 importance of PET, the usefulness of PET to assist in
4 the early diagnosis of dementia. So the committee
5 has not formally met but several of us on the
6 committee are extremely supportive of the position
7 that I have made today.
8 DR. SOX: Thank you very much. Yes, sir.
9 Please come to the mike, introduce yourself and --
10 whoops, you have been here before, Dr. Conti, so just
11 say who you are for the benefit of the reporter.
12 DR. CONTI: Peter Conti again. I have
13 listed my credentials and conflicts earlier. I
14 actually have a question for Dr. Albert and I would
15 like -- perhaps I'm the only one in the room that
16 maybe is misunderstanding the issue or maybe there is
17 a conflicting statement here, but from what I

18 remember about this type of request of class drugs is
19 that these are in fact investigational, they are
20 off-label uses of unapproved pharmaceuticals. Is
21 that still correct?
22 And if in fact we're dealing with an
23 investigational drug, and we're classifying PET as an
24 experimental procedure, why is the Alzheimer's
25 Association pushing an investigational drug in an
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1 experimental procedure they's not pushing? And then
2 why is it that they use PET, or she uses PET, which
3 is still considered investigational, in a certain
4 subset of patients? So, I would like her to clarify
5 that.
6 DR. SOX: Dr. Albert, would you like to
7 respond and then we will go ahead with break as soon
8 as you're done.
9 DR. ALBERT: I was trying to make a
10 distinction between the position of the Alzheimer's
11 Association and what we do clinically, and the
12 position of the Alzheimer's Association is that we
13 feel that the standard clinical procedures for
14 evaluating patients is the current way that patients
15 should be evaluated, and that all of the imaging
16 modalities that are currently available are still in
17 an experimental phase with respect to diagnosis.
18 What we do clinically, what I do
19 clinically in my own setting is a separate issue.
20 DR. SOX: That's fine, thank you. You can
21 have the discussion during the break if you like.
22 DR. GARBER: Maybe Dr. Albert can respond
23 to the investigational. Are these drugs
24 investigational?
25 DR. ALBERT: There are currently three
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1 medications that are on the market for the treatment
2 of AD and memory disorders, and there is a good deal
3 of evidence that people who have substantial
4 cognitive impairment but don't yet meet clinical
5 criteria for dementia have underlying pathology of
6 AD, and that's the reason that some clinicians
7 throughout the country that I know of offer those
8 medications to individuals. Not because we know that

9 they will definitely be beneficial, but because it's
10 possible that the may be, and there are currently
11 trials underway, as was already mentioned.
12 DR. SOX: So at this point, has the FDA
13 approved --
14 DR. ALBERT: It has approved three drugs
15 for the treatment of AD.
16 DR. SOX: Approved for that purpose.
17 DR. ALBERT: Absolutely.
18 DR. SOX: Thank you very much.
19 DR. HOLOHAN: And to reiterate again,
20 Dr. Albert, you said PET or SPECT.
21 DR. ALBERT: Yes, I said PET or SPECT.
22 DR. SOX: Thank you. We will now take a
23 ten-minute break. Don't go too far, please.
24 (Recess taken from 10:33 to 10:47 a.m.)
25 DR. SOX: The next step in the process is
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1 discussion among the committee, which will lead to a
2 motion and a vote. I would like to remind everybody
3 in the room that this, we can ask for people to help
4 us with our discussion but it's not in the ground
5 rules for people to volunteer to help us in our
6 discussion. So if we want you, we will call upon
7 you, but it's basically the business the committee is
8 transacting in public, which is a little different
9 than what has been has happened before.
10 And so the plan goes something like this,
11 that we will first of all, I'd like to have Barbara
12 and Frank address the issue about the question that
13 was considered, and I will read the original
14 question, the revised question. You can just kind of
15 explain what your thinking was, and I will also ask
16 Sean if he wants to comment on that.
17 Then I am going to ask Dr. Matchar to
18 comment on any of the issues that were raised by the
19 speakers in the previous session. Then we will
20 discuss any evidence about the interpretation of the
21 evidence, although I want to point out that mostly
22 what we will be doing there is teeing up issues for
23 the coverage group itself to take into account when
24 they make their coverage decision, and only under
25 exceptional circumstances would we remand this issue

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1 back to the panel on the basis of interpretation of
2 the evidence.
3 Then I'm going to ask everybody, starting
4 with Randel and going around the room, to make any
5 last comments they would like to make on this issue
6 and then I will ask for a motion and we will vote.
7 So that's the plan. And there will be no lunch until
8 we're done.
9 (Laughter.)
10 So, I'd like to read from the minutes of
11 the Diagnostic Imaging Panel. First I will read the
12 original question. A motion was made and seconded to
13 vote on the following question: Is the evidence
14 adequate to demonstrate that PET has clinical benefit
15 in evaluating patients with suspected AD? And the
16 underlying word is suspected.
17 The question that they actually voted on
18 was exactly the same, except that instead of
19 suspected, it said possible or probable AD, and then
20 afterwards, as defined by the current American
21 Academy of Neurology guidelines. So that's the
22 difference between what was teed up and what you
23 finally voted on.
24 So, Frank and Barbara, could you tell us
25 what it was that led you to make this change? And I
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1 think the real issue for us as an executive committee
2 is, was this an error, an important error in process
3 to have made this substitution. That's what we
4 really have to judge, so perhaps you can explain why
5 you did that, and we can form our own judgments.
6 DR. McNEIL: Hal, I will explain what I
7 think is the non-difference between the two areas,
8 and then the issue of why the change was made that is
9 in the minutes, and maybe Frank will comment on that.
10 First of all, I'm glad Leslie asked the
11 question and I'm glad that Dr. Silverman clarified
12 what he viewed as the areas of suspected AD, and as I
13 listened to his remarks there were four, four
14 components to that. One was dementia, with or
15 without a documented diagnosis of AD, and these are
16 the words he used. The second was possible or

17 probable Alzheimer's. The third was MCI, which 50 to
18 80 percent of the time led to incipient AD. And the
19 other was memory complaints, which 10 percent to X
20 percent, I don't remember the upper bound, went to
21 incipient AD.
22 Now as I look at those four components and
23 look at the definition of the words possible and
24 probable, I think possible and probable includes all
25 of those things, particularly since suspected AD
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1 disease is not a disease with a diagnosis of 100
2 percent, it's either possible or probable. So if it
3 were definite, then I would agree that there might be
4 a mismatch, but there's no such thing as 100 percent
5 positive predicted value of AD from what I gather
6 from reading this literature and hearing the
7 testimony today.
8 So that, I would say that the difference
9 between the two is nonsubstantive.
10 DR. SOX: Frank, do you want to comment?
11 DR. PAPATHEOFANIS: I really don't have
12 anything more to add. I think that covers it.
13 DR. SOX: So, Barbara has asserted that
14 this change is nonsubstantive. Is there anybody on
15 the panel who would like to challenge her on that
16 point? Because, if not, I don't think we have a
17 quarrel with the process. Anybody want to challenge
18 that? Leslie.
19 DR. FRANCIS: I don't want to challenge
20 it, but I just want to understand that -- I took it
21 that the commentator was saying well, you just looked
22 at a narrower class, so you know, you looked at the
23 class where it was less likely to be helpful as an
24 adjunct. But you're saying no, we understood the
25 larger class and we made that clear.
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1 DR. McNEIL: That's exactly right, Leslie,
2 and I think that the words in fact in the four
3 components document that.
4 DR. SOX: Now I would like Sean then to
5 comment on -- I'm sorry, Bob, I didn't see you.
6 DR. BROOK: If that's the case, would it
7 be proper to amend the recommendation that you guys

8 made, maybe just put in a footnote that says this
9 includes suspected, whatever the language was, AD?
10 DR. PAPATHEOFANIS: Sure, that's
11 reasonable.
12 DR. BROOK: I mean, because if the
13 committee believed it to be the same and we are
14 voting on the same recommendation, is that within our
15 purview of process, to put in parentheses that this
16 means, this includes suspected AD?
17 DR. SOX: Alan.
18 DR. GARBER: Well, I share the sentiment
19 that it's important to document what was meant, but I
20 but I would propose that be reflected in the minutes
21 and it will certainly be in the transcript, what
22 Frank and Barbara just said, so I don't think it's
23 necessary for us to try and go back and change
24 anything the panel said.
25 DR. SOX: Since it's not a substantive
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1 change, I agree with Alan. I think that the minutes
2 provide adequate documentation, or will provide
3 adequate documentation of their thinking, and it's
4 almost a legalism.
5 DR. BROOK: Which minutes?
6 DR. SOX: The minutes of this meeting.
7 DR. BROOK: So the minutes of this meeting
8 will include explicit statements that the panel
9 included suspected, the chair people believe or
10 whatever, the panel included a belief that would
11 state firmly that suspected was included as a
12 subcategory of possible or probable.
13 DR. PAPATHEOFANIS: Yes.
14 DR. BROOK: Thank you.
15 DR. SOX: Sean, I would like you now to
16 comment on the second question that you raised about
17 MCI. Can you tell us what your thinking was there?
18 DR. TUNIS: In hearing this discussion and
19 then also in reviewing the transcript of the
20 diagnostic imaging meeting, we did spend a lot of
21 time on this taxotomy issue of what exactly we were
22 voting on. We had a lot of input at the time from
23 Dr. Silverman as well, and we seem to have done a
24 vote on the possible and probable dementia, using

25 that phraseology. Then we had another separate vote
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1 on mild cognitive impairment that came out
2 unanimously the same way.
3 Then there was a supposed hole that was
4 left of something that wasn't addressed that I think
5 that I'm just going to read from the transcript,
6 Dr. Silverman's comment, and see if we can at least
7 get clarification if we're leaving anything out here,
8 because if we are, I know it will come back to
9 trouble us when we try to actually develop our policy
10 on this. And since Dr. Silverman is here, maybe he
11 can help us work through this.
12 I wouldn't use the words probably
13 Alzheimer's. That has a very specific definition as
14 assigned by, I don't know if it's NIH or AAN, which.
15 American Academy of Neurology. But they actually
16 probably have Alzheimer's is what we would say.
17 There's also a hole that's being left here if you
18 consider just MCI and just possible and probable AD,
19 because there are many people who have dementia who
20 would qualify by DSM-III or IV criteria as having
21 dementia who still wouldn't have possible Alzheimer's
22 or probable Alzheimer's.
23 So before going beyond that, maybe
24 Dr. Silverman, if you could help us define, what is
25 the hole that's still being left after we have
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1 covered possible probable Alzheimer's as well as MCI,
2 what else is left?
3 DR. BROOK: And suspected.
4 DR. SILVERMAN: Yes. This goes first of
5 all to the error that Dr. McNeil made just a few
6 minutes ago when she said that she thought that the
7 possible and probable would be encompassing to
8 suspected. In fact it was explicitly said and it was
9 added to these words, possible and probable as
10 defined by the American Academy of Neurology current
11 recommendations, and so that explicitly does not
12 include people who have dementia but don't have
13 possible or probable, and it explicitly does not
14 include people who have age associated memory
15 impairment and so forth. It was very clear that it

16 was meant to apply to this focus group.
17 And then to have an ad hoc say, you know
18 decision that we will go back and say it really
19 applied to everybody when the debate didn't focus on
20 that is I think a very unfair thing to do as well.
21 So the hole that's being left very explicitly in the
22 case of dementia, are people who do have dementia,
23 that is as several people defined it, that they have
24 more than one cognitive domain being affected, that
25 they have evidence of progression that's seen over a
.00107
1 period of time, and that it involves them to the
2 point that they have functional impairment. It will
3 include some people who will then go on by the
4 American Academy of Neurology recommendations to use
5 the ADRDA criteria to include people who have
6 probable AD, and it will include some people who have
7 possible AD, and it will include some people who have
8 dementia but don't meet the criteria for either
9 possible or probable AD, and those people were never
10 even voted on, and we explicitly asked them to be
11 voted on, and there was a refusal to vote on them at
12 that time.
13 DR. HOLOHAN: I'm unclear, I'm sorry.
14 DR. SOX: I am too. Again, what is the
15 hole that wasn't plugged?
16 DR. SILVERMAN: That people who meet the
17 criteria for dementia as defined by DSM-III or IV
18 criteria, but don't meet the criteria, which are more
19 profound for AD as defined by the ADRDA and NIDCS
20 criteria, which is the criteria that the American
21 Academy of Neurology uses to define possible and
22 probable AD. In other words, there is a whole host
23 of things that can cause dementia, Alzheimer's is
24 just one of them. It's the most common, but there
25 is -- some of the other ones were referred to today.
.00108
1 Dr. Albert talked about frontal temporal dementia.
2 Those patients wouldn't meet possible or probable AD
3 criteria necessarily, depending on exactly how they
4 present clinically. There is dementia that can be
5 caused by a whole host of disorders that may or may
6 not get detected by other tests that are being done

7 in order to try to rule them out and if they are
8 detected, at the very least, it will turn a probable
9 into a possible. But depending on what they find, it
10 may even knock it out of the possible and probable
11 category all together. So, AD is one of about 25
12 different disorders that are known to cause dementia,
13 and those other patients are not being voted on.
14 DR. TUNIS: I guess the question is, what
15 is the data that's relevant to that patient
16 population that would have been the subject of a
17 vote? What's the information base that people were
18 supposed to be considering for that subgroup which is
19 at least somewhat hard to explain, and I'm wondering
20 if it's been defined enough to actually bring some
21 data to the table. And I don't know if Dr. Matchar
22 has any thoughts about this, because I know
23 Dr. Matchar struggled with these taxotomies as well
24 in doing the model, so maybe he has some way of
25 helping out with this after you.
.00109
1 DR. SILVERMAN: The data is the great
2 danger that everybody in this room agrees upon, or at
3 least that's been spoken to, and seems to agree upon,
4 of having a patient who actually might have AD, their
5 brain is actually going through deterioration, of
6 cholinergic impairment and so forth, they actually
7 might have AD but they don't meet the criteria for
8 being diagnosed with AD, and so they don't get
9 properly treated --
10 DR. BROOK: They don't meet the criteria.
11 You have to use these words specifically; otherwise,
12 you're not helping your case. They don't meet the
13 criteria for even possible AD.
14 DR. SILVERMAN: For even possible AD as
15 defined by the American Academy of Neurology's
16 acceptance --
17 DR. BROOK: Where is that definition, or
18 what is it? I can't find it in any of the materials
19 we have.
20 DR. SILVERMAN: That definition appears as
21 a consensus recommendation of the National Institute
22 of --
23 DR. BROOK: What is it? Can you specify

24 it? What are the components of it so I can
25 understand precisely the group of people. Because
.00110
1 they voted on mild cognitive impairment, and they
2 voted on possible Alzheimer's. Now what's between
3 mild cognitive impairment, which they unanimously
4 voted no, and possible Alzheimer's, which they
5 unanimously voted no, what falls in between those two
6 categories?
7 DR. SILVERMAN: People who have any of the
8 other 25 possible diagnoses that you think are
9 causing their dementia. Maybe Dr. Small can clarify
10 that a little bit.
11 DR. SOX: Do you want to speak, get to the
12 microphone and try to help us here?
13 DR. SMALL: Let me try to clarify these
14 points. As I said, dementia in a sense is a severity
15 diagnosis, okay? So you have, before dementia you
16 have mild cognitive impairment. These are people who
17 have --
18 DR. BROOK: They voted no on that.
19 DR. SMALL: Well, I'm just trying to
20 clarify the definitions for the committee, okay? So
21 mild cognitive impairment is people with memory loss
22 that may have other cognitive impairments somewhat,
23 but it's not interfering with daily life, so that's
24 not quite dementia. As that progresses, people get
25 dementia. Now if you have dementia, as I pointed out
.00111
1 in my pie chart, about 55 percent, I think we all
2 agreed on a figure like that, have AD.
3 When we say AD, we mean probable AD as
4 well as possible AD. Now if you include the
5 possibles, maybe it's 60 percent or some confidence
6 interval there, but basically probable and possible
7 AD were clearly defined in 1984 by the so-called
8 MACAN criteria or the NIND/CDS/ADRDA criteria
9 published in Neurology in 1984 where you need
10 impairment in memory, impairment in other cognitive
11 domains, interferes with daily function and it
12 gradually progresses. It is very well laid out. If
13 it's probable AD, it's very clear.
14 If it's possible, it means that there is

15 something atypical about the course, there's a
16 secondary illness, there's a bit of a question, but
17 that's quite different from suspected dementia where
18 there you are including, or dementia in general is
19 that other 45 percent, which could be depression, it
20 could be frontal temporal, it could be Lewy body.
21 And then if you're going to suspect a dementia, then
22 you might even include MCI as well.
23 And you know, the other issue I just
24 wanted to mention is that the AAN committee, they
25 looked at those criteria, and also the AAN committee
.00112
1 is against treat all, clinicians are not treating
2 all, it's not happening, it's against the standard of
3 care.
4 David Matchar, help us out.
5 DR. MATCHAR: You want me to make comments
6 about this specific point alone?
7 DR. SOX: This specific issue, and then we
8 need to get through this issue and then we can talk
9 about other issues.
10 DR. MATCHAR: Well, again, we understood
11 up front that patients who are going to be going
12 through a clinical evaluation of some quality,
13 hopefully guided by the American Academy of Neurology
14 recommendations but perhaps not exactly, were going
15 to be evaluated as having suspected, possible,
16 probable, about 55 percent of those we assumed were
17 going to actually have AD, and that was actually the
18 base case analysis. We acknowledged that about 45
19 percent of these people are not going to have AD and
20 so the analysis that you all saw and evaluated was
21 based on the notion that if patients were going to be
22 evaluated as well as clinical clinicians currently do
23 in the community, which perhaps is about 55 percent
24 positive predicted value, that it makes sense to go
25 ahead and treat those individuals based on a full
.00113
1 typical clinical evaluation. Not to treat them
2 simply because they walked in the door and said you
3 know, I have a problem with my thinking, but because
4 you've evaluated them to the level of your ability as
5 a typical clinician based on your reading of the

6 American Academy of Neurology guidelines.
7 So that's really it. I mean all of these,
8 the discussion about what does it mean to be
9 possible, probable and so on, we never were able
10 to -- you know, we have those listed as appendices in
11 the technical report, and I frankly don't really
12 understand what subgroup is being discussed here.
13 But I think that we subsume this question under the
14 sense that the baseline analysis of which a large
15 minority of individuals don't have AD.
16 DR. SOX: What I heard was that there is a
17 spectrum of cognitive impairment, from MCI to
18 dementia.
19 DR. MATCHAR: Right.
20 DR. SOX: And once you get into the
21 dementia category, then you could have possible or
22 probable Alzheimer's as the cause, and that sounds
23 like it would cover everything from the zero
24 probability of Alzheimer's to 100 percent probability
25 of Alzheimer's, and then you could have other causes
.00114
1 of dementia besides AD.
2 DR. MATCHAR: Well, one specific thing
3 that was assumed a priori was that secondary and
4 particularly reversible causes of dementia were being
5 evaluated, and that is part of the American Academy
6 of Neurology recommendations. What's left over then
7 is things that are not treatable. I don't know if
8 that's answering the question.
9 DR. SOX: I guess the question that's been
10 raised is have we failed in using the words possible
11 and probable to describe the spectrum of likelihood
12 that the patient has AD? Have we somehow missed some
13 group? Deb, do you want to comment?
14 DR. ZARIN: Could I try to clarify one
15 thing? Clinically the model started, there was an
16 MCI and an asymptomatic group, but talking about the
17 group with mild dementia, it started with a diagnosis
18 of mild to moderate dementia based on the AAN workup.
19 So once you diagnose someone as being demented, which
20 has to do with cognitive impairment and functional
21 problems, then there is a differential diagnosis of
22 dementia. One of the diagnoses possible is

23 Alzheimer's. But then it was just said, there are
24 25, whatever number of possible causes of dementia
25 there are were subsumed in the other 45 percent.
.00115
1 So the model dealt with this by saying
2 okay, we know you have mild dementia. We are
3 assuming based on sort of a common clinical workup
4 that I think it was 56 percent of you will be
5 ultimately proven or if you could prove it, would
6 have Alzheimer's. So you have that other 44 percent
7 who have all those other, so that was how we dealt
8 with it in the model.
9 I don't know if that helps, but just think
10 about the diagnosis of dementia separate from then
11 trying to find out the cause of the dementia.
12 DR. SOX: Bob.
13 DR. BROOK: I understand what you did and
14 I think I understand what I'm hearing. But we have
15 to figure out some wording here to reconcile this.
16 Let me try to explain it. What I here the clinicians
17 testifying is they want to know whether Frank and
18 Barbara's group explicitly considered those people
19 that meet the diagnosis of dementia, they have more
20 than mild cognitive impairment but the clinician is
21 not willing to say they even have possible
22 Alzheimer's. He is absolutely fully confident they
23 have frontal temporal disease, or depression or
24 something else, Alzheimer's is not even possible by
25 the neurology definition.
.00116
1 And he wants to do a PET scan for those
2 people, presumably I would guess to find out whether
3 they have Alzheimer's patterns, not to rule out
4 Alzheimer's, and then treat them, and they would not
5 offer therapy for this group where clinically the
6 evaluation at the end of it is, well, clinically the
7 evaluation at the end of their evaluation is not even
8 possible Alzheimer's, so there is no justification
9 for treating those people clinically. But they want
10 to do something else and if the PET scan is positive,
11 they would treat them.
12 I think that's what I'm hearing. Does
13 that make any sense?

14 DR. ZARIN: Well, the problems with that
15 is that the treatment studies as I understand it,
16 have used essentially the AAN workup to select people
17 to go into the treatment trial. So they say, let's
18 say, we have 200 people who we have done this workup
19 on, and they meet the criteria for what I'm calling
20 mild dementia, okay? We are putting 100 of them into
21 some standard treatment arm and 100 of them into this
22 cholinesterase inhibitor arm. And on average the
23 cholinesterase inhibitor arm did better than the
24 other arm. We don't know if a different way of
25 selecting those patients would have led to a better
.00117
1 outcome, so it's a non-answerable question.
2 The argument being that if we could figure
3 out which 45 didn't have Alzheimer's, that they would
4 be better off not getting the treatment is
5 unanswerable, that hasn't been done.
6 DR. BROOK: I just want to rephrase. I
7 want to know whether the panel explicitly considered
8 those people where the clinician, and we have heard
9 only from tertiary centers, where after a tertiary
10 center referral, the doctor says, Dr. Small says this
11 person has no -- he has dementia but doesn't even
12 meet the possibility of having Alzheimer's, and he
13 would like to do -- and I don't know what proportion
14 of his patients fall into that group, but he has no
15 possibility of having Alzheimer's but he would like
16 to do a PET scan for that group of patients. That's
17 what he said.
18 You explicitly voted out the impairment
19 before they get to dementia, and you explicitly voted
20 out possible or probable. But I'm asking, that other
21 group of patients, did the committee explicitly make
22 the recommendation about them? And Barbara said yes,
23 and it was refuted on the basis of the fact that they
24 don't fall into this.
25 So, is this for anyone? Can we get rid of
.00118
1 this? Is this possible or probable Alzheimer's, or
2 do we mean anyone with suspected dementia? What did
3 the committee decide?
4 DR. McNEIL: I think this is a question of

5 wording and that we are really getting caught up in
6 the words that we're using. I think that the
7 committee functionally looked at a combination of
8 scenario A and scenario B, and those two scenarios
9 together encompassed both.
10 DR. BROOK: So the minutes of this meeting
11 ought to reflect that not only did we look at
12 possible or probable Alzheimer's, but the committee
13 also looked at suspected dementia, not suspected
14 Alzheimer's, and concluded from their analyses that
15 all three of these categories, mild cognitive
16 impairment, selected dementia of any type, and
17 possible or probable Alzheimer's, that PET scan was
18 not worth doing.
19 DR. McNEIL: I would say that was the
20 intent of the committee.
21 DR. BROOK: Okay. Can the minutes so show
22 that, of this meeting?
23 DR. SOX: The minutes will reflect that.
24 DR. BROOK: And that plugs the hole.
25 DR. SOX: I think that deals with the
.00119
1 issue that we have been struggling with for the last
2 10 or 15 minutes. Okay.
3 Now I would like to move the discussion on
4 and give David a chance to comment on any other
5 methodologic or interpretive issues that were raised
6 during the public presentations.
7 DR. MATCHAR: Well, I did just want to
8 thank you, Frank and Barbara, for presenting both the
9 model that we did and obviously the discussion during
10 the previous meeting very succinctly and well, and
11 I'm glad I wasn't responsible for doing that.
12 But, I think a few points that I just want
13 to reiterate. One is that it really was very
14 important in this analysis that we separated out
15 these levels, the demented patients, the mild
16 cognitive impaired patients, and the patients who are
17 concerned because of a strong family history, and
18 that the focus of the group clearly was on the
19 symptomatic patients because that's the area in which
20 the clinical research has been done regarding
21 treatment. That is, patients who have been in

22 clinical trials, as Dr. Zarin mentioned, are all
23 patients who are symptomatic, not mild cognitive
24 impairment, although there are ongoing trials, and
25 not patients who have first degree relatives,
.00120
1 although their lifetime incidents of dementia is
2 extremely high; if people live long enough in that
3 population, they probably will develop AD. So these
4 were very important that we separated them out.
5 The primary conclusion, again for the
6 symptomatic patients, was driven by the point that
7 Frank made earlier which is, if you have a patient
8 with dementia who you might otherwise based on AAN
9 criteria, based on clinical treatments have treated,
10 if you impose a test on those patients and place that
11 as a criteria for whether they receive treatment or
12 not, then some number of those patients will not get
13 treated, and that number is probably on the order of
14 about 10 percent, and I think that the data that was
15 presented earlier, the new abstract based data that
16 was presented earlier, I think also is consistent
17 with that, that about 10 percent of patients who had,
18 who ultimately developed dementia will be PET
19 negative.
20 So what you have done is guaranteed that a
21 certain number of people are not going to get a
22 treatment that's been shown to be effective. But
23 that's for the symptomatic population.
24 For the other populations, again, the key
25 element is that we don't know that treatment works in
.00121
1 that population and I think in more general terms
2 with regard to PET, that there's no evidence even in
3 the dementia population that a PET scan predicts
4 treatment responsiveness, and I think that's really
5 key, because that's part of the logic that I was
6 understanding, that we want to treat people who do
7 not satisfy AAN criteria for dementia because there
8 is a very strongly held feeling that if you had a
9 positive PET scan, you will respond to treatment
10 because those people have AD and treatment works
11 because you have AD. It may indeed by true that the
12 only reason people respond once they are symptomatic

13 is because they are symptomatic; it may not be that
14 these drugs will work to help people in delaying the
15 onset of dementia.
16 So, that is the testable hypothesis that
17 is being tested. Certainly, I don't know if indeed
18 it's being tested in the first degree relatives of
19 Alzheimer's patients, but certainly it would be
20 worthwhile doing.
21 So, I think that there were three things
22 that we don't know that would keep us, that I felt
23 based on the analysis, would keep us from being able
24 to be optimistic and positive about the use of PET
25 scans in the current situation. One is of course, as
.00122
1 I mentioned, that we don't know whether PET positive
2 patients who don't yet have dementia are in fact
3 treatable, that's unknown. We don't know whether PET
4 predicts treatment responsiveness even among patients
5 who do have dementia, so that's an unknown. And the
6 issue that was raised about whether primary care
7 physicians would do a better job if they used PET
8 scans, and one of the suggestions was perhaps we
9 ought to just forget about sending patients to a
10 neurologist or to the cognitive impairment center,
11 but rather just sending them for a PET scan.
12 By the way, CMS does pay for these
13 evaluations by neurologists and by Alzheimer's
14 specialists, so you want to use this presumably as a
15 substitute. Well, we don't know that if primary care
16 physicians had a PET scan available, that they would
17 treat any more quickly or they would treat a larger
18 number of people. I would wonder if indeed it was
19 true that a PET scan would lead a primary care doctor
20 to more appropriately treat symptomatic patients who
21 should be getting treatment anyway, is there
22 potentially a less expensive was of doing it than by
23 sending them to receive a PET scan. So in other
24 word, if primary care docs aren't already doing the
25 right thing, can we get them to do the right thing
.00123
1 short of spending the $2 or $3,000 to do a PET scan.
2 And I apologize for raising the issue of
3 dollars, because we specifically avoided that, but

4 it's certainly a resource intensive thing to do.
5 So, that's my comments.
6 DR. SOX: Okay, questions? Leslie.
7 DR. FRANCIS: This is actually a question
8 both for the diagnostic imaging panel and for you,
9 and it goes to the treat-all strategy. When I was
10 sent this list of general discussion questions, there
11 is a lot more texture to them than what the panel
12 finally voted on. The general discussion questions
13 ask, are there specific groups of patients, what
14 other issues which haven't been identified, and so
15 on. And as I tried to work out the logic just as a
16 layperson, it seemed to me that your biggest worry
17 was the false negative possibility as against the
18 treat-all strategy, that is, that the downside of
19 adding PET was that some people wouldn't get
20 appropriate care and that roughly assumed sort of a
21 balance between people who get care when they
22 shouldn't and people who don't get care when they
23 should, which rests on the idea that treatment
24 actually is relatively benign.
25 Now, suppose you had a group of patients
.00124
1 who had been identified by the standard clinical
2 workup and started treatment on the treat-all
3 strategy. They had been, say, being treated for
4 several months. It isn't yet clear what the effect
5 of the treatment is going to be on cognitive status,
6 but side effects are clear. I mean, there are some
7 folks who do have side effects from these drugs.
8 Would it then make sense to try to do a PET scan,
9 saying oh, look, we're less worried about a false
10 negative here because of the fact that this is a
11 patient who is experiencing side effects.
12 I'm just trying to figure out whether
13 there might have been groups of -- I don't know what
14 other groups of patients the panel looked at, what
15 other considerations the panel raised, because that
16 didn't filter through to me in the summary here.
17 DR. MATCHAR: Well, this is a clinical
18 question that I think I should defer to those who are
19 involved in clinical care of patients with AD and who
20 use these drugs. But my understanding from our

21 interviewing experts in the area was that individuals
22 who are having side effects, the side effects we're
23 talking about are the ones that are sufficient to
24 cause someone to want to stop the drug, and that
25 there didn't seem to be sort of a very thin line that
.00125
1 needed to be discerned between those who should stop
2 and those who shouldn't stop. And indeed, it's
3 something that could be evaluated as a separate
4 question, is there a subpopulation for whom their
5 dysutility or loss of quality of life because of side
6 effects counter balances whatever improvements in
7 quality of life they are going to receive from
8 therapy.
9 DR. SOX: Bob.
10 DR. BROOK: David, let me pose another
11 clinical scenario. A large number of Medicare
12 patients don't have drug coverage. This drug costs
13 $1,200 a year. If Medicare covered PET scan, and
14 since you can't tell -- I mean, this drug doesn't
15 improve function, it just prevents it from declining
16 slightly, and the side effects and others. Are there
17 a group of patients who if you really did a utility,
18 would say that hey, I'm willing to, if the PET scan
19 is negative, and the government paid for it, I would
20 not put out of my pocket $1,200 a month, a year, for
21 medication.
22 And did the panel consider -- this is not
23 explicitly considering costs, but it is a question of
24 whether you believe, you know -- what I'm trying to
25 get at, I mean, I believe that one of the problems of
.00126
1 this field is that immediately upon approving
2 anything, every person over the age of 50 is going to
3 get a PET scan but the question is -- just like they
4 do with heart scans on everybody -- but the question
5 is, on the other side, are there groups of people
6 from what you know about utility analysis, decision
7 analysis, where you can postulate that there would be
8 people that would see the sensitivity and specificity
9 of this test, and did the panel explicitly consider
10 those subgroups of people that might use it to make a
11 different decision? Why should they put out of their

12 own pocket $1,200 a year in medication.
13 DR. MATCHAR: Well, perhaps you ought to
14 turn to Alan Garber about this, but I think that my
15 response would be that you're actually asking us to
16 explicitly incorporate the dollars because you're
17 dealing with an issue of willingness to pay, and
18 there's a question of what somebody considers, and
19 it's an economic issue.
20 DR. BROOK: Not for the test. I am
21 talking about in the utility function as an outcome.
22 DR. MATCHAR: What utility are you talking
23 about? Is it the --
24 DR. BROOK: The patient makes a choice
25 that they would rather buy food than pay for Aricept.
.00127
1 MS. RICHNER: Did you consider that in
2 your decision analysis?
3 DR. MATCHAR: Well, I think -- would you
4 be willing to respond to that question?
5 DR. GARBER: Well, I will tell them what I
6 think your study did. You were not instructed to
7 look at that question, and therefore, you didn't, and
8 I don't think any of us could say what the answer
9 would be to your question, Bob. I think it's a
10 question, it's a reasonable question to ask, but it's
11 sort of irrelevant to our deliberations today,
12 because I don't think whether a patient might want
13 the test for some reason has ever been the basis for
14 us making a decision. So Bob is just saying well, if
15 they have to lay out this money for the drug, would
16 it be maybe, you're asking would it be cost effective
17 to do the test in that context, but that's not rally
18 the way that we judge any of the technologies that
19 come before us and that's not what we asked David's
20 group to.
21 MS. RICHNER: One of the concerns that I
22 was thinking about, if the person had a positive
23 diagnosis with the PET scan, it was approved,
24 whatever, would they be willing to tolerate the side
25 effects of the drug regime, you know, be a little
.00128
1 more aggressive and a little more willing to stay on
2 the therapeutic intervention for a while knowing the

3 trade-off and knowing that they had a confirmed
4 disease.
5 DR. SOX: Well, if some day there is good
6 solid evidence to that effect, then we can
7 reconsider, but right now there is no evidence other
8 than sort of anecdotal and common sense reasoning,
9 which doesn't -- Deb.
10 DR. ZARIN: But it also, I think that your
11 question assumes, at least if you were thinking of a
12 rational patient, that the test is a better way of
13 predicting whether you are going to get benefit from
14 the drug or not. In other words, if you knew that
15 the test actually could predict whether you were
16 going to respond to the drug better than the clinical
17 workup, then that seems like a logical question to
18 ask, could it help me decide to save my money,
19 whether it's relevant for this committee to ask or
20 not. But we don't know that the test is better at
21 predicting who is going to respond to the drug or
22 not. That experiment hasn't been done.
23 There is reason to believe that some
24 people without Alzheimer's but with other things in
25 the differential respond to cholinesterase
.00129
1 inhibitors, so it is not at all clear that the test
2 is a good way to predict who is going to respond.
3 DR. SOX: Bob.
4 DR. BROOK: I'm not asking that question.
5 I'm asking a person, I'm not saying it has to be
6 better. I'm saying that I could as a rational person
7 say this neurologist is really a fake and his
8 sensitivity and specificity is not that great, and I
9 want both. If I'm going to put out the $1,200 a year
10 for this drug, I want both a combination of a good
11 clinical workup that says I have Alzheimer's, and a
12 PET scan that says I have Alzheimer's, because either
13 one of them has error in it, and that's what I want.
14 And I just want to make sure that, I mean, it sounds
15 like these kinds of subgroups were not included in --
16 I mean, that's really a very rational thing to do.
17 So it's like saying that if I do an
18 angiography and I know that one reader has a 70
19 percent reliability, I want two or three readers, and

20 if I put those two or three readers together, I may
21 increase my specificity and I may miss a case or so,
22 but I'm willing to do that, I'm willing to make that
23 trade-off before I get my chest cracked. So that's
24 what I'm asking you, David, are there cases where
25 these things would both be positive where some
.00130
1 rational person would say if I have to pay for it,
2 that I would be only willing to pay for it under
3 those circumstances?
4 DR. MATCHAR: I think that what you are
5 describing is a circumstance that is entirely, it is
6 a utility or a psychological perception, it's
7 something that somebody decides in their mind that if
8 they were to receive something that they perceive to
9 be objective as opposed to being something that --
10 DR. BROOK: Isn't it because --
11 DR. MATCHAR: (Inaudible, multiple
12 speakers.
13 DR. BROOK: Let me just ask the question
14 this way. Isn't it the case that if I'm positive on
15 a good clinical exam and positive on an independent
16 PET scan, that the probability that I really have AD
17 is higher than if I'm positive on either one of them?
18 Isn't that known?
19 DR. MATCHAR: No.
20 DR. SOX: I just want to say, we really
21 need to wrap up this conversation and get on to other
22 people, so let's try to answer and then let's move
23 on.
24 DR. MATCHAR: Well, just to answer your
25 question, the simplest part of your question which
.00131
1 is, did we include this explicitly, and the answer is
2 no.
3 DR. SOX: Okay. Barbara.
4 DR. McNEIL: Well, I guess one of the
5 things as I was thinking about this, Bob and others,
6 all of the issues that have been raised by Randel and
7 by Bob, really in the simplest form boil down to some
8 kind of utility. I mean, that's really what they're
9 coming down to, however we could integrate all of
10 these factors, they come down into some kind of

11 utility assessment. And the issue there is, is there
12 any way that we could believe that all of these would
13 get to a utility so low that it would flip people
14 into the test strategy rather than in the treat
15 strategy. I mean, that's really, if you boil it all
16 down, that's what it comes to.
17 So what I did actually in preparation for
18 this meeting is review the article by Chapman and
19 Neumann, which many of you may have seen, that
20 summarizes the utility literature to date across
21 consumers and caregivers and the lay public. And in
22 fact it's very hard to get very low. I mean, if you
23 have death and you've got total paralysis and stuff
24 like that, you can get down to the zeros, but most of
25 the things that we're talking about don't really hit
.00132
1 that low. So when I read this, and I actually
2 requested the article so I'd be sure I was up to date
3 on these utilities, I think it would be hard, I
4 really think it would be hard taking into Randel's
5 concern and your concern that we pull the utility
6 down so that we cross that threshold line. And we're
7 never going to know, because we don't have those data
8 specifically for Alzheimer's patients. The data that
9 I'm quoting are for a whole slew of patients, so if
10 we wanted to make these utilities Alzheimer's
11 specific, we'd have to go out and do several really
12 quite large studies.
13 DR. SOX: Wade, you have been waiting to
14 ask a question, so go ahead.
15 DR. AUBRY: My question related to
16 Leslie's, and that was the clinical situation, and it
17 was just sort of a comment Leslie had said, if the
18 patient had been treated for several months and was
19 having side effects. And I think speaking as a
20 clinician, generally you would know within a shorter
21 period of time whether there would be some clinical
22 improvement based on the drug, and then there would
23 be a clinical decision about whether the side effects
24 outweigh the benefit. And so, that sort of gets back
25 to the usefulness of the clinical evaluation.
.00133
1 So, I guess the question in regard to PET

2 would be, you know, if you make a decision to stop
3 the drug, would a PET scan be useful in that patient?
4 You have a patient who's had a clinical improvement,
5 and that is really sort of beyond the scope of what
6 we're doing here.
7 DR. SOX: Yeah, beyond the scope, no
8 evidence. Other issues that people would like to
9 raise for David?
10 DR. TUNIS: David, I think it was
11 Dr. Small, I believe, maybe Dr. Silverman today,
12 talked about and actually some of their slides showed
13 some of the studies that suggested, you know, delay
14 in nursing home placement or other outcomes
15 associated with at least treating, I'm not sure about
16 testing, where there was potential improvements
17 associated with an accurate diagnosis and treatment.
18 And I don't think those kind of outcomes were
19 included in your model. So for example, better
20 caregiver arrangements, delayed admission to nursing
21 home, fewer repeat visits for evaluation and testing,
22 those sorts of things, and I'm just wondering, was
23 that a body of literature that you looked at in terms
24 of preparing the model or if not, why not, or does
25 the model in any way address those sorts of outcomes?
.00134
1 DR. MATCHAR: I know of no literature and
2 we didn't identify any literature that demonstrated
3 that PET scan results in some way allowed people to
4 make better plans for their lives beyond what could
5 be done by having a patient evaluated by a
6 neurologist expert in this field. But there is
7 evidence that that kind of advice is very useful, but
8 not that PET scan will influence the use of those
9 interventions.
10 DR. SOX: What I would like to do now by
11 way of focusing the discussion or perhaps finding
12 that we're ready to vote is to have each person kind
13 of state what their thinking is on this issue, where
14 they are, recognizing again, and just to remind
15 everybody that our job is to decide whether the panel
16 followed good process, interpreted the evidence that
17 was in front of them in a reasonable way.
18 And so, Randel, would you start please?

19 MS. RICHNER: I have my five seconds in
20 the sun here, but I just wanted to say that I think
21 what concerns me more than anything else, and Bob
22 briefly touched on that, is the emphasis on whether
23 an adjunctive diagnostic test, and this is very
24 generic in a sense, must lead to a change in
25 treatment pattern or a change in health outcome, and
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1 it's a fundamental concern. I think that if all
2 tests had to go, diagnostic tests had to go through
3 this level of scrutiny, the radiology labs would be
4 pretty quiet.
5 So, I think that this is very fundamental
6 here in terms of how we're evaluating this but given
7 that, I know we have to get back to our question
8 here, what we're evaluating, PET. Considering what
9 the question was, and that's also a concern in the
10 process, how we're evaluating the question, how we're
11 deciding the question, what evidence we're going to
12 need for that question, I would say that I have to
13 agree that at this point there is little evidence
14 that supports there would be a change in treatment
15 associated with this.
16 DR. SOX: Frank, you can second guess your
17 own panel if you want.
18 DR. PAPATHEOFANIS: I guess I'm not going
19 to comment on our process. I think you know what the
20 committee decided and I think I defined that.
21 DR. SOX: Wade.
22 DR. AUBRY: I think that the question that
23 was framed was appropriate, and I think the concerns
24 that were raised by the speakers about the actual
25 question that the panel reviewed was adequately
.00136
1 answered, so I feel comfortable with that. I also
2 feel that the approach used by the assessor from Duke
3 was sufficient and more compelling than the evidence
4 that was presented today during the presentation.
5 So, I feel that in terms of addressing the questions
6 and in terms of the process of the imaging panel,
7 that I would be in favor of upholding their vote.
8 I also think it's significant, I don't
9 think my decision hinges on this, but I do think it's

10 significant that the official statement of the AAN
11 does not recommend PET in the routine evaluation of
12 these patients, and that the official position of the
13 Alzheimer's Association is that this is an
14 experimental procedure. Again, that's not the major
15 determining factor in my view, but I think it is a
16 significant piece of additional information.
17 DR. SOX: Leslie.
18 DR. FRANCIS: Since we're advisory, I
19 actually have a question that I just want to be sure
20 that I've got the answer from the folks from the
21 Diagnostic Imaging Panel, and that's their answer to
22 question two of the CMS questions. Were there any
23 other issues not addressed in the model that you all
24 thought in the panel discussions might influence the
25 decision to use PET that we haven't heard about? I
.00137
1 mean, have we gotten out on the table everything we
2 need to know in answer to that question from your
3 deliberations for CMS to now listen to?
4 DR. PAPATHEOFANIS: Right. I think the
5 questions that you're referring to, the genesis of
6 those are through the Agency, and they were intended
7 to stimulate thought when folks received the package,
8 and were really I think very useful in that context.
9 But to answer your question specifically, no, I think
10 everything was on the table and the minutes reflect
11 that.
12 DR. McNEIL: I would agree, Leslie. I
13 think in particular you might be talking to some of
14 the psychosocial of legal issues --
15 DR. FRANCIS: Well, yeah.
16 DR. McNEIL: -- that were addressed
17 specifically in Table 10, and were specifically
18 commented on during the course of the deliberations.
19 DR. SOX: Bob.
20 DR. BROOK: In general, I agree, yes. I
21 would reiterate a position that I have stated many
22 times before. I am sure that a well done up-front
23 sort of appropriateness analysis where we really
24 looked at subgroups would find subgroups where
25 decision analysis would support using a PET scan in
.00138

1 these groups of people with the current evidence
2 that's available, and I think we drew out a few of
3 those cases. I think it's probably in this case
4 small, but I hope that the process in the future
5 could become more sophisticated in identifying these
6 subgroups explicitly and explicitly modeling or using
7 judgment to figure out what to do. But given where
8 we started from, I think the subcommittee did a
9 commendable job.
10 DR. SOX: And if there were such subgroups
11 discovered and published in the peer reviewed
12 literature, then the coverage group could modify
13 their coverage policy.
14 DR. BROOK: I disagree. We've had this
15 disagreement before and I won't let that go. I
16 believe it's important that this panel and this
17 process take the best expert clinicians and use state
18 of the art technology up front to identify explicitly
19 the clinical subgroups that people are interested in,
20 with explicit definitions, and the vague kind of
21 questions that are given to the panel don't do that,
22 and the methodology for doing this has advanced for
23 the last 15 years. It's just like you used decision
24 analysis methodology here; that methodology ought to
25 be used in this process up front. I think until we
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1 do that, good clinicians will not necessarily believe
2 the kinds of results that we produce. They can be
3 combined.
4 DR. SOX: John.
5 DR. FERGUSON: Well, I suppose until we
6 have trials of diagnostic studies that have outcomes
7 and are randomized and so on, that we will fall back
8 on modeling, and I think that this model that the
9 Duke people came up was quite novel, at least in my
10 view. I was impressed by it. What hasn't been
11 discussed here so much but is implied in their Table
12 10 of the Matchar report was, the specificity in the
13 PET scan studies comes out to be around 75 percent.
14 I realize that that's supposed to be better than the
15 usual clinical thing, but the patients that I see are
16 terrified of having a diagnosis of AD most of the
17 time, and their families are, so I think that a false

18 positivity of 25 percent is not insignificant, and I
19 wonder how the people who use PET scans a lot handle
20 that, but that's sort of an aside.
21 I think the panel did a good job in using
22 modeling to come up with a reasonable answer.
23 DR. SOX: Thank you, John. Barbara.
24 DR. McNEIL: It would be hard for me to
25 say the committee didn't do its job, but I would say
.00140
1 actually that we did from several perspectives, and
2 just integrate some of the comments that have been
3 made so far.
4 First of all, I think we responded to a
5 level of detail in the request that was made by those
6 individuals requesting coverage so that we didn't get
7 down to really tiny subgroups, we were responding in
8 general to a general request. And had the
9 formulation of the questions discussed at a previous
10 meeting before a subcontractor was even hired for
11 this process is my understanding, and then we asked
12 that subcontractor to answer questions that had been
13 publicly vetted using criteria that the MCAC had
14 developed over the past year and a half. Right or
15 wrong, those are the criteria and is what we had to
16 go by.
17 And the subcontractor in my view, you did
18 a terrific analysis that was really state of the art
19 in all possible ways of decision analysis, and
20 integrated the literature in a very sophisticated
21 fashion and therefore, came up with a conclusion that
22 I think was robust, given the givens. I think what
23 the issue so far that has been raised is, wouldn't it
24 be nice if we were able to get some more specific
25 subgroups or some more specific questions. And maybe
.00141
1 the thing that the audience can do is say ah hah,
2 there are some very specific issues that were raised
3 and those issue are the ones that we should go
4 research and get answers to, and then perhaps feed
5 back in the form of another kind of request. The one
6 that comes to mind was the predictability of PET in
7 assessing the response to the cholinesterase
8 inhibitors. So it would be that kind of thing that I

9 think an analysis of this may be helpful for, despite
10 it's nonenthusiastic acceptance I suspect, by members
11 of the audience.
12 DR. SOX: Daisy.
13 DR. ALFORD-SMITH: I too would be in
14 support of the committee's recommendations and would
15 also like to commend them for a job well done, I
16 think it was great.
17 My decision was based upon not only the
18 analysis that was provided by the subcontractors and
19 how the panel took that into consideration, but I
20 also found it interesting, particularly in reference
21 to what Dr. Albert said, and she had the ability to
22 differentiate what she was doing in a clinical
23 setting but yet stepped forward in terms of making a
24 recommendation on behalf of the Alzheimer's
25 Association. And then lastly, my conclusion was
.00142
1 based on how the subcommittee made the decision to be
2 inclusive in terms of various definitions without
3 leaving that perceived gap within that whole process
4 and so based upon that, I support it.
5 DR. SOX: Alan.
6 DR. GARBER: I agree with everything
7 that's been said, but I especially want to echo one
8 of Barbara's statements. We have a number of very
9 distinguished researchers in this area in the
10 audience today, and I was struck by how useful it
11 would be to have a study that directly addressed the
12 differences between outcomes when care is managed by
13 the standard AAN approach and adding PET, and I think
14 that if we had good studies of that kind, and you
15 could even look at treatment of individuals in whom
16 the standard workup and PET were discordant, it
17 doesn't have to be a huge study, but I think it would
18 be enormously helpful in trying to determine the role
19 of PET, and we just don't have that yet.
20 But I think the committee clearly did
21 their job, and I didn't take the panel's
22 determinations or any other work to say that this
23 test does not have a future for Alzheimer's disease,
24 it's just given what we know now about the tests and
25 about the treatments, it doesn't meet the criteria

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1 that we've set up.
2 DR. SOX: Tom.
3 DR. HOLOHAN: I generally agree with Alan.
4 I would simply add one comment about the issue raised
5 of subcategories of patients who may differentially
6 benefit. We have seen this in this committee and in
7 the subpanels in issues where it's easier to make
8 that distinction, and that's in treatment. My own
9 panel looked at litologous stem cell transplants in
10 high dose chemotherapy for multiple myeloma, and then
11 later at levo-carnitine use in end-stage renal
12 disease patients. And when you have varying and
13 usually more or less small response rates, it's easy
14 post hoc to speculate that there may be some
15 subcategory of patient that may benefit but the fact
16 is that there is no evidence available to allow you
17 to take that beyond the level of speculation, and I
18 think that's kind of what Alan was addressing about a
19 prospective study.
20 To force CMS to consider the possibility,
21 unproven, that there are subcategories that may or
22 may not respond when in fact the evidence is not
23 available that would allow you to make that
24 distinction, I think is totalogy.
25 MS. BERGTHOLD: I just want to make a
.00144
1 comment about the Alzheimer's Association's
2 thoughtful response to the panel and to note that I
3 believe this is the first time that any advocacy
4 organization has actually, has actually not advocated
5 for the coverage of the device or the technology, and
6 I thought that was an interesting and balanced
7 response on their part. I myself have encouraged
8 consumer organizations to look at, you know, to
9 really look at the whole spectrum of possibilities
10 when they are coming before us, to not just advocate
11 for coverage of something, but to look at sort of who
12 it would harm, who it would help, and really on
13 balance what the outcomes would be. So, I would just
14 like to note that for the record.
15 DR. SOX: If I get to vote, I will vote to
16 ratify. I think the committee followed the process

17 very nicely and interpreted the evidence that they
18 got in an appropriate fashion. One of the advantages
19 of decision analysis is that it tells you what the
20 variables are that are likely to really make a
21 difference in making their decision, and I think we
22 have tended to focus the discussion on the key
23 variables in this particular problem, and hopefully
24 as we use decision analysis in the future, we can do
25 so in the same way.

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1 I guess the other comment is that we are
2 also sticking pretty much to the rule of evidence
3 here and we have been pretty careful about ruling out
4 of bounds questions such as testing in patients who
5 have a clinical condition for which there is no
6 proven therapy, and in Alan's calling for a
7 randomized controlled trial of management with or
8 without the test, I think we are trying to push the
9 envelope on the evidence and we will probably be back
10 in a couple years with this problem.
11 So with that -- do I turn it over to you
12 at this point?
13 MS. ANDERSON: I have a brief comment.
14 DR. SOX: Before we vote, I would like to
15 give anybody a chance in the audience, a chance to
16 step up to the microphone and for a maximum of two
17 minutes say anything that they would like to
18 influence the outcome, but two minutes maximum.
19 Please identify yourself, state any conflicts.
20 DR. PHELPS: Mike Phelps, UCLA. I have
21 some ownership in a company, CPI. I do not receive
22 money from anybody other than that so I have no other
23 conflict.
24 There are two comments I would like to
25 make. One is that dementia is not a disease, it is a

.00146

1 clinical syndrome of symptoms or signs. The issue
2 here is that both for good clinical management and
3 use of treatment and by the FDA label, in the mild to
4 moderate stages you have to make the differential
5 diagnosis, and PET is the most accurate way to do
6 that. We keep ignoring the fact that clinical
7 diagnosis goes on for years, and it has a lower

8 accuracy than PET at the start of that, when they are
9 actually at that stage. The clinical diagnosis
10 accuracy comes after they have progressed to later
11 stages.
12 The other comment I would like to make is
13 just a general comment that if you treat everyone and
14 in a broader category at the earlier times, aren't
15 you telling all of them that they have AD? What is
16 the implication of that? We said at the early stage,
17 about 30 to as high as maybe 50 percent of the people
18 have things other than AD. The good molecular
19 therapy, pharmacologic therapy, is to identify
20 patients that have cholinesterase deficits when you
21 give them a cholinesterase inhibitor, and that's the
22 liability and responsibility that one has to step
23 forward with, and PET is a great aid to the
24 physician, not to replace them but to assist them in
25 making that at a very early mild to moderate stage as
.00147
1 opposed to just saying well, we're going to give you
2 the drug and then the implication of that, that I
3 don't know yet that you have a cholin deficit, and by
4 giving you the drug that I think you have
5 Alzheimer's.
6 MS. ANDERSON: For today's panel meeting,
7 voting members present are Daisy Alford-Smith, Wade
8 Aubry, Robert Brook, John Ferguson, Leslie Francis,
9 Alan Garber, Barbara McNeil, Frank Papatheofanis, and
10 Tom Holohan. Chairperson Hal Sox will vote in the
11 event of a tie. A quorum is present, no one has been
12 recused because of conflicts of interest. At this
13 time the chairperson, Dr. Hal Sox will call for a
14 motion and will ask the voting members to vote.
15 DR. SOX: Would anybody like to make a
16 motion that we can act on? Tom.
17 DR. HOLOHAN: I move that the executive
18 committee accept the recommendations and conclusions
19 of the Diagnostic Imaging Panel.
20 DR. ALFORD-SMITH: Second.
21 DR. SOX: We have a motion and a second.
22 Any further discussion before we vote?
23 MS. ANDERSON: I'm going to read the
24 entire motion. The motion is to accept the

25 recommendations of the Diagnostic Imaging Panel
.00148
1 regarding the use of positron emission tomography
2 (PET) for the diagnosis and patient management of
3 Alzheimer's disease and other dementias. Those
4 voting members voting to agree, or for.
5 DR. FRANCIS: I think I need to state for
6 the record since I came late, that I have no
7 conflicts.
8 MS. ANDERSON: Those against? And no one
9 has been recused and no one is abstaining, so it is
10 unanimous for.
11 DR. SOX: At this point I would like to
12 declare a recess. We'll reconvene at five minutes to
13 one.
14 (Recess from 11:55 a.m. to 1:05 p.m.)
15 DR. SOX: I would like to call the
16 committee to order please. This afternoon we're
17 going to have I guess what's considered to be an
18 educational program on the role of decision analysis
19 in coverage, our advice about coverage decisions.
20 Some of you might think that we're going
21 about this a little backwards in having a relatively
22 entry level discussion of a topic that we have
23 explored in such a sophisticated way this morning
24 with David Matchar's talk. The purpose of this
25 session, at least the purpose or my talk, which is
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1 going to be an introduction, is really for people to
2 kind of understand at a gut level the rationale
3 behind using decision analysis in coverage decisions.
4 And if you're like me, sometimes you'll
5 here a presentation that sounds extremely logical but
6 you really don't understand what's going on in the
7 engine room, and you sort of nod and it sounds
8 logical, and you accept it. So what I'm going to try
9 to do is talk a little bit about what's going on in
10 the engine room, and then Dave is going to take the
11 discussion up several levels, and hopefully when
12 we're done with this, we will have a much better
13 understanding of how decision analysis can help us in
14 the many instances in which we don't have high
15 quality data.

16 So, if you look at our interim
17 recommendations for operating policy, you'll see that
18 we're told to pay attention to the validity of the
19 evidence, and we all recognize that the ideal is to
20 have several randomized trials that all point in the
21 same direction, but frequently we are dealing either
22 with discordant trials or with observational studies
23 in which the assembly of the cohorts that you're
24 comparing may be made more difficult by selection
25 bias or by confounders that are influencing both the
.00150
1 tendency to get the intervention as well as the
2 tendency to have the desired outcome. We're also
3 told to pay attention to the applicability of the
4 evidence to Medicare patients and finally, we're told
5 to pay attention to the magnitude of the effect of
6 the candidate for coverage relative to already
7 covered options.
8 Now, I posit that the role of decision
9 analysis in coverage decisions boils down to
10 something we heard implicitly in discussion this
11 morning. If high quality trials aren't available,
12 decision decision analysis is the next best option
13 for measuring effect size, for evaluating the role of
14 bias and confounders, and extrapolating the evidence
15 to other populations. So that's sort of what I'm
16 asserting. Just a reminder. Confounder is an
17 influence or factor that both influences the tendency
18 to get the intervention on the left, and also
19 independently influences the outcome so that the
20 intervention and the outcome are moving in the same
21 direction, and you are tempted to make the inference
22 that it's the intervention that's affecting the
23 outcome, when in fact it's the confounder that's
24 moving both in a coordinated fashion.
25 Now, the basic principle of effective
.00151
1 expected value decision making is a sort of principle
2 of utilitarian philosophy, which is always choose the
3 decision option that has the highest expected
4 outcome, and by expected outcome we really mean the
5 highest outcome on average if you were faced with
6 that decision many many times, you would pick the

7 outcome that would turn out the best in the long run.
8 A decision tree is a method for assessing the balance
9 across arms and benefits, basically a way of modeling
10 a management strategy.
11 Now I have been fond of using a metaphor
12 for expected value decision making that makes an
13 analogy with gambling. One play at the slot machine,
14 an individual gambler has no way of knowing how
15 things are going to turn out. But a year of play at
16 the slot machine, which is what the casino owner has
17 to deal with, you know very precisely what's going to
18 happen, because there will be tens of thousands of
19 repetitions and under those circumstances the play of
20 chance is actually very predictable.
21 Now applying this metaphor to the doctor
22 who either has one patient for which he has to make a
23 decision or on the other hand, the other perspective,
24 namely that of casino owner, is a lifetime of
25 practice, and what you should be doing if you're an
.00152
1 expected value decision maker as a physician is to
2 choose or encourage the option that leads to the
3 greatest gain in the long run, that is to say, the
4 option that over a lifetime of practice would provide
5 more benefits to the patient than the alternative.
6 Now calculating expected value is a pretty
7 straightforward process. Here we illustrate a game
8 of chance in which you have the option, if you choose
9 to play the game, there's a 10 percent chance of
10 winning $100, a 30 percent chance at $10, and a 60
11 percent chance of having to pay $60, and the question
12 is should you play. The symbolism here, the circle
13 represents a chance node at which the outcome is
14 driven by chance. If there were a square, it would
15 indicate a decision node, at which the decision is
16 either yours to make or the decision would be to
17 choose the option with the highest expected outcome.
18 So the way that you calculate the expected
19 value at this chance node is to multiply the
20 probability of each outcome times the magnitude of
21 the outcome, so here we have .1 times 100, plus .3
22 times 10, plus .6 times -60, and it turns out
23 narrowly if you play this game many many times you

24 will come out about $4 ahead. So, when David Matchar
25 pushes the button on the computer to do a
.00153
1 calculation, it's doing many many calculations of
2 this type.
3 DR. BROOK: I think you did your math
4 incorrectly.
5 DR. SOX: I could go backwards to dispute
6 this but if I did, we'd be in big trouble. Okay.
7 Did I make a mistake?
8 DR. BROOK: Yeah, you set it up so .3
9 would make it worth playing the game, but that's all
10 right.
11 DR. SOX: Well, if that's the worst
12 outcome that happens in this talk, I will be okay. I
13 knew I'd do something like that, and I knew that you
14 would say something about it, Bob.
15 (Laughter.)
16 DR. SOX: So now let's take kind of a
17 hoked up clinical example and walk through this hoked
18 up clinical example. This is a man who has a slow
19 growing malignancy surrounding his aorta, which is a
20 bad place to have a malignancy. He's been told that
21 he has two years to live if nothing else happens, and
22 the question is should he go for curative surgery or
23 palliative surgery, or optionally, simply accept the
24 two-year prognosis. Now the way I've set this up,
25 radical surgery looks pretty bad. There's only a 50
.00154
1 percent chance of surviving this operation, which is
2 one that's being done in a very delicate part of the
3 body, and there's only about a 50 percent chance of
4 cure if he survives the operation. Whereas,
5 palliative surgery has no chance of a cure, but
6 improves somewhat, but has a very good chance of
7 surviving the operation. So the question is, which
8 option should he prefer?
9 Now here we represent a model of the
10 decision and the square represents the decision,
11 which is try for cure or palliate. And if you try
12 for cure, there is a substantial chance of operative
13 death represented by the first chance node, and then
14 as you go to the right, there is the long-term

15 outcome of the operation which is whether there is a
16 cure or no cure. And the tree has the same structure
17 on the bottom, but as you will see, the numbers will
18 be different.
19 Now the factors in a decision tree are
20 pretty straightforward. There is the probability of
21 the chance outcomes and then there is the outcomes
22 themselves, and the key thing of course is you want
23 to use the same measure or same unit throughout the
24 tree. One outcome you could use is life expectancy,
25 which is the average length of life. Alternatively
.00155
1 you could use utility, which is a number, which is a
2 measure of preference for an outcome, usually
3 expressed on a zero to one scale, or you could use
4 quality adjusted life expectancy, in which you
5 multiply life expectancy times utility, which in
6 effect converts years in an unhealthy state if it was
7 life expectancy only, into years in a healthy state.
8 And finally, you could use the word that we don't use
9 much around here, which is cost.
10 So here I put the probabilities on the
11 tree, and here I put the outcomes on the tree. The
12 life expectancy of 20 years if there is a cure, life
13 expectancy of two years if effectively the operation
14 doesn't alter the prognosis.
15 Now this slide shows how you would
16 actually average out at a chance node and then fold
17 back the tree to calculate the expected value of the
18 two decision options. So in the upper right chance
19 node, you would multiply the probability of cure,
20 0.5, times the life expectancy, 20 years, and add
21 that to the probability of no cure times the life
22 expectancy of two years; that gives you 11 years,
23 which you then multiply times 0.5, and then add the
24 0.5 times life expectancy with operative death, which
25 is zero, and that gives you 5.5 years on the average
.00156
1 that you would experience if you tried for the cure.
2 In the bottom part of the tree you can see that the
3 average length of life would be about two years.
4 So, although this doesn't look like a
5 particularly good gamble for the patient to take to

6 try for a cure, in fact it's the best of a bad
7 situation, according to this analysis.
8 Now, one of the most important parts of
9 decision analysis is sensitivity analysis, which is a
10 method you can use to decide if one of these factors,
11 either the probabilities of the outcome measures
12 could alter a decision. And the basic approach in
13 sensitivity analysis is to first establish a range of
14 reasonable values for the factor such as probability
15 or outcome measured, and then you substitute the
16 lowest value in the range of reasonable values into
17 your decision model, and calculate the expected
18 value. Then you repeat the calculation but now
19 substituting the highest value in the range and you
20 ask yourself, does the preferred decision option
21 change as you go from the lowest to the highest value
22 in the range. If it doesn't, then you can conclude
23 that the decision is not sensitive to that factor.
24 So that's the basic principle behind
25 sensitivity analysis, and Dave showed us a very
.00157
1 elegant example of two-way sensitivity analysis in
2 the presentation this morning.
3 Now sensitivity, I think can help coverage
4 policy a lot. For example, if you think that there
5 might be selection bias, then you could postulate an
6 effect of selection bias that could change the
7 preferred option. Or if you think there's an
8 unmeasured confounder that could be making it
9 difficult to have an unambiguous interpretation of an
10 observational study, you can postulate an unmeasured
11 confounder and its effect, and then ask for either
12 one of these, how large of an effect of these two
13 factors would be needed in order to change which
14 option is preferred, and if that effect is
15 outlandishly large, then you could conclude with at
16 least a moderate degree of confidence that those
17 biases and confounders would not be important.
18 It can also help in trying to apply
19 findings in one population to an older Medicare
20 population. For example, you could model the effect
21 of older age on life expectancy as an outcome
22 measure. An older person has a shorter time to live

23 and has other diseases that are likely to prove fatal
24 while waiting for all the benefits of an intervention
25 to play out in the form of greater life expectancy,
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1 and you can model that very nicely with decision
2 analysis. You could also postulate an effect of age
3 on the effectiveness of the candidate technology and
4 again, ask yourself, how do these changes in the
5 factors in the model alter the effect of the
6 candidate technology.
7 So, I'll finish up with just a couple
8 slides on cost effectiveness analysis, which
9 conceivably could be in our future sometime later on.
10 Alan Garber has described cost effectiveness analysis
11 as a method designed to assess the comparative impact
12 of expenditures on different health outcomes, so it's
13 a way of comparing several different potential
14 interventions and trying to decide basically, are you
15 going to get your money's worth from an intervention
16 that's more expensive.
17 The basic approach is comparative. You
18 compare the cost of the proposed intervention with
19 the cost of the currently accepted technology, and
20 you divide that by the difference in quality adjusted
21 life years with the candidate technology as compared
22 with the existing technology. Now cost effectiveness
23 analysis, therefore, measures the impact of a
24 candidate technology on cost and outcomes. It's
25 always comparative and it measures an effect relative
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1 to the status quo. The CEA yard stick that's in
2 common use is that less than $50,000 per additional
3 quality adjusted life year is considered to be
4 reasonable, 50 to 100,000 is considered to be a gray
5 area, and more than $100,000 is expected to be an
6 expensive policy to apply over a large population.
7 Just where those numbers come from is something that
8 Alan is going to explain if anybody is interested.
9 Finally, you can do decision analysis of
10 testing, and that's really what David did in his
11 analysis, and here's an example of a choice between
12 testing, treating everybody, or observing and neither
13 testing nor treating. And I have just modeled to

14 show that if you choose the test option, the test
15 could be positive or it could be negative; clearly,
16 that's a matter of chance. And if the test is
17 negative, the patient could either have the disease
18 or not have the disease, and we could have that same
19 disease no disease chance option in any of those
20 branches that don't have anything attached to them,
21 and then model the effect of changing the probability
22 of disease and see which of the three options has the
23 highest expected value for different probabilities of
24 disease, and define the zones of probability in which
25 each are preferred, as David inferred earlier.
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1 So, the role of decision analysis in
2 coverage decisions is mainly when the only evidence
3 is from observational studies and you need to try to
4 stitch together evidence from different observational
5 studies and then try to model the effect of
6 confounders, model the effect of applicability to
7 Medicare patients, and of selection biases, and when
8 you want to assess the potential impact of unmeasured
9 effects.
10 So, that concludes my brief presentation,
11 hopefully a look inside the engine room for those of
12 you who don't know this field and for those of you
13 who do know the field, an opportunity to skewer your
14 chair with a great question. Nobody is going to take
15 the opportunity to skewer me. Sean.
16 DR. TUNIS: I will try to skewer the
17 chair. The question is, in the example that you gave
18 of the malignancy around the aorta, it obviously
19 raises the issue that I think kind of underlines some
20 of the discomfort with the decision model applied to
21 the PET Alzheimer's case too, which is the lack of --
22 well, in that case, the lack of patient preferences
23 as part of the calculation. So for example, I may be
24 interested as an individual in a 98 percent chance of
25 living two years rather than taking a 50-50 chance of
.00161
1 being dead right after the operation or during the
2 operation, I guess.
3 And so, which raises I guess some issues
4 around coverage policy, because the preferred

5 strategy in aggregate there was the five years to do
6 the surgery versus the 2.99, but for an individual,
7 it might be appropriate based on their preferences
8 actually to not do the surgery, and I'm just
9 wondering if you could comment about that in terms of
10 addressing it through modeling and policy.
11 DR. SOX: Well, one way to -- you know, a
12 policy, a decision to cover on the basis of the
13 effects over a large number of patients kind of opens
14 the doors for patients and clinicians to do it if
15 it's clinically important. But for an individual
16 patient, you would like to model their personal
17 preferences which might, and one person might have
18 very different preferences than another. Now some of
19 the time the preferences won't make any difference,
20 and that's one of the nifty things about sensitivity
21 analysis, you can assume a utility of 1 for an
22 outcome or a utility of .5, and if the preferred
23 option is the same over that range of utilities, then
24 you ought to be really coming on pretty strong in
25 recommending that to the patient, because it's
.00162
1 unlikely that their preferences should affect their
2 decision making.
3 On the other hand, if it's a close call
4 and the preferred option changes as you go from a
5 utility of .9 to 1, then you ought to pay a lot of
6 attention to what the patient is telling you in
7 making your recommendation. But I think the
8 difference between a policy which opens the door and
9 individual decision making is really very nicely
10 encompassed by a decision model of this type where to
11 develop the policy you might use utilities that have
12 been obtained by doing a study of 500 patients and
13 getting the utilities, but when you apply it in
14 patient care, you use the patient's utilities.
15 Any other questions for me? John.
16 DR. FERGUSON: Did you mean to suggest
17 that soon we will be taking up cost effectiveness
18 analysis for our debates?
19 DR. SOX: I don't know of any plans for
20 that.
21 DR. TUNIS: I don't think he was

22 suggesting that.
23 DR. SOX: I certainly wasn't suggesting
24 that, but my guess is that some day we're going to
25 get around to using cost in our decisions, in which
.00163
1 case we will need to go over this again.
2 DR. FERGUSON: Thank you.
3 DR. SOX: Well, if there are no further
4 questions, then I will turn it over to Dave Matchar.
5 DR. BROOK: Hal, can I ask you one
6 question? Is anyone ever going to put together the
7 science of the reliability of the decision analysis
8 process? If you give the same problem to two
9 different teams, how consistent they approach it, I
10 would just like to point out for the panel, that kind
11 of work has not been done. And just because it's
12 quantitative and looks simple, it's not; it requires
13 skill an delicacy to do these things and I don't know
14 of any literature in which the same problem has been
15 subjected starting from scratch, by two decision
16 analysis teams, and the way they've gone through the
17 literature, come up with the sensitivity, what they
18 have done, how they have modeled it out and actually
19 produced comparable results.
20 And the reason I bring this up is because
21 all of the quantitative types on this panel bemoan
22 the fact that expert clinical judgment and
23 appropriateness and all that process which has a
24 known liability to it at least, because those tests
25 have been demanded, there are no tests that I know of
.00164
1 the other form of work that's been done, and I would
2 urge that this field -- you know, we may want to
3 adopt this technique and I have nothing against it,
4 but I would urge that the reliability of this process
5 done independently by different teams of different
6 merit and skill should be assessed.
7 DR. SOX: I actually know of one example,
8 but it's unpublished, under review, and actually in
9 that one at least, there are pretty consistent
10 results in that particular one. Of course, it's not
11 independent, because one came before the other.
12 DR. BROOK: I would make one other case,

13 that it's very hard sometimes, just like you see in
14 the material, it's really hard to go through all of
15 the work that has been done, especially when this
16 comes out as a computer program, and there are
17 mistakes that have been made. When we have looked at
18 some of the modeling, for instance, of the decisions
19 about using coronary angiography in bypass surgery,
20 there were things that didn't make any sense, like
21 there was no immediate death rate from surgery
22 following bypass surgery, and we couldn't figure it
23 out. And we go back, and the database they used
24 happened to have no deaths over the first hundred
25 patients. So yes, there are sensitivity, there are
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1 analyses, but when you start getting complex things
2 here, it does require devotion to the kinds of stuff
3 that you've done in your career, which is really
4 meticulous paying attention to detail and reading
5 through what the assumptions of the decision analyst
6 is who's doing this.
7 DR. SOX: Yeah, reviewing a really complex
8 decision model can be virtually an impossible task,
9 and I have seen decision models, one by Alan and one
10 by Steve Powker on a very complex issue where you
11 basically had to say this person has good reputation,
12 and that's it. One think that would be nice would be
13 if we could get to the point where somebody who is
14 submitting a decision analysis for publication would
15 send the model, and it would give a few brave souls
16 an opportunity as reviewers to play with the model to
17 see how well it behaves at some of the extreme ends
18 of the ranges of assumed value. Barbara.
19 DR. McNEIL: This is sort of an example,
20 an answer to your question, Bob. When we had the
21 Diagnostic Imaging Panel in January, Peter Neumann
22 was one of the advisors to that panel and he told us,
23 and Frank, correct me if I'm wrong, that he and his
24 colleagues were actually developing a similar model
25 and when he looked at this one closely, he found out
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1 that both his model and the Duke model had
2 essentially the same structure, and differed ever so
3 slightly on that relative risk. Duke was .72 and he

4 was .70, or something, and so at least for that
5 situation --
6 DR. BROOK: And I didn't point out the
7 calculation problem just to be a pain in the ass. We
8 did raise -- we always run out of money on these
9 things and when we did the Rand -- you know, we spent
10 $100 million doing the Rand health insurance
11 experiment, which was the most major health services
12 randomized trial ever done, and there was no money
13 ever to double independently code tens of thousands
14 of line items that we coded when we reversed all
15 these variables, did all the regressions, selected
16 the variables and did all this stuff. They were
17 never double coded; they were double key punched,
18 they were double checked, but never double
19 independently coded, and Joe Nuast to this day has
20 nightmares about if somebody would say, I want to go
21 back, take exactly the raw data set you had, and
22 independently, using exactly the same logic,
23 translate that into computer code and then see if you
24 get the same results.
25 We tend to run out of money at that time,
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1 and one of the things that we will need to discuss as
2 we do this is, you know, after you specify the model
3 and do all this stuff and you turn it over to a
4 computer analyst or a software package to do it, I
5 mean, simple mistakes produce errors, and unless you
6 go through them, you can't find them. And as you
7 say, going through some of these models, nobody
8 really ever does in detail. I just think it's stuff
9 that we have to be aware of.
10 DR. SOX: We will turn things over to Dave
11 Matchar, who is going to take things up several
12 notches.
13 DR. MATCHAR: Well, my job is to assuage
14 all your concerns, obviously. This is a very
15 daunting task. The discussion here is going to be
16 about your bringing what I call quantitative
17 modeling, so I'm using a term more broad than
18 decision modeling. Quantitative modeling to the
19 processes that you are engaged in in developing
20 recommendations for CMS.

21 Again, I'm using a more general term,
22 clinical policy formation. I feel that I'm bringing
23 coals to New Castle. This is a group where many of
24 you have been working in this area for years and have
25 been concerned about the question of when and whether
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1 to use quantitative modeling, but you asked me to
2 talk and so I will.
3 So I will just give you some of my general
4 observations based on not only this work, and I will
5 try to allude to the work on PET scanning where I
6 think that it relates to some of the questions that
7 you just raised, and other questions as well. But
8 also, I'm going to be basing these comments on
9 experience I've had and interactions I've had with
10 other people who have worked in the area of using
11 quantitative assessment, quantitative modeling in
12 policy formation both in and outside of the clinical
13 or medical realm.
14 Steve Powker being one person who I've
15 spent some time talking with some years ago. He was
16 involved in working with the NIH consensus panels,
17 trying to consider ways in which consensus
18 development might be improved through the use of
19 decision modeling. I don't believe that it
20 ultimately got incorporated in the long term, but
21 there were some exercises that were published out of
22 that. And also, I have some experience working with
23 someone in a business context, namely Larry Phillips
24 at the London School of Economics, and also Dr. Bill
25 Asher, who is in public policy, and much of the work
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1 that he did is in the area of general public policy,
2 and the issues he's been concerned with has been how,
3 what have been the successes and failures in the
4 application of quantitative analysis in policy
5 formation, and I think those kinds of studies have a
6 lot of relevance here.
7 Now, the overall goal I have here is to
8 convince you indeed that there really is a role of
9 quantitative analysis in your deliberations, and it
10 may or may not be in the area of using expected
11 utility decision making.

12 A couple of slides just to kind of warm
13 you up a little bit is definitional. First of all,
14 what's clinical health policy, both because the
15 center that I direct is called the Center for
16 Clinical Health Policy Research, and people wonder
17 why did you add the word clinical instead of just
18 health policy. But also really because we're talking
19 about clinical health policy development in this
20 area, as opposed to more general public policy.
21 Who are the policy makers and what do they
22 want? Well, that should be self evident; it's you,
23 but there are other health policy makers and they do
24 want different things. But then fairly quickly I
25 will try to move on to the question at hand, which is
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1 quantitative health policy models, what are they, how
2 can they help make better health policy decisions and
3 more specifically, how should models be incorporated
4 in the policy making in the MCAC.
5 Now, clinical health policy, the
6 definition that I apply here is it that it's
7 decisions that relate to the clinical enterprise. It
8 can be somewhat indirect, as in the case of your
9 group, your concern with decisions that have to do
10 with how physicians practice medicine, how patients
11 receive care. They can be the decisions themselves
12 you're concerned with, should a woman between 40 and
13 49 seek mammograms, should physicians recommend
14 carotid noninvasive tests for asymptomatic
15 individuals? Or it can also be issues that relate to
16 the health system, structures which support those
17 decisions, such as electronic medical records in
18 anticoagulation clinics.
19 And the distinction that I'm making here
20 is, and it's maybe idiosyncratic my using the term,
21 but I think the public policy is often really not
22 specifically intending to deal with clinical causal
23 relationships, but may often deal with clinical
24 issues as a black box. So why this is relevant here
25 in the area of your deliberations is that I think
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1 that much of what you're concerned with require the
2 careful input of clinicians in the entire enterprise.

3 While the health policy makers are
4 everybody, of course, and I only list this taxotomy
5 of micro, meso and macro just to make that point,
6 that everybody does want to make decisions, everybody
7 does make decisions, but I think there is a more
8 important issue to make, which is that when decisions
9 are being made at these various levels, there is an
10 opportunity depending on how the analyses are done,
11 for them not to be concordant with one another, or
12 not to be consistent with one another, and I think
13 that fundamentally, one of the concerns that
14 certainly I suspect you all are interested in is as
15 people at the macro level, that what you produce is
16 something that is also consistent with the other
17 levels as well. You don't want to be making
18 determinations that are inconsistent in that sense
19 because as I'm sure you have discovered on multiple
20 occasions, that is the formula for disaster.
21 What do health policy makers want? Now,
22 you notice I haven't yet talked about quantitative
23 policy modeling, because to me the issue really isn't
24 about the models. I mean, we can talk about the
25 models and I will talk about the models, but really
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1 we're talking about the policy making and the policy
2 makers, that's really what the subject is here. And
3 then secondarily, can we use quantitative techniques
4 or any other techniques for that matter, to
5 facilitate the decision making process.
6 And so in answering this question, we're
7 talking now about having a client or a customer if
8 you want to use those terms, they're the health
9 policy maker, what do they want, that's the first
10 question you should ask. And whatever anyone might
11 say about you all, I believe that you as health
12 policy makers want to do the right thing. I hope
13 that makes you feel good. What does that mean?
14 Specifically to evaluate uncertain and controversial
15 issues in a calm and rational environment. The kinds
16 of decisions that you are faced with often are going
17 to be very stressful for everybody involved.
18 Stopping, taking a breath, being able to think
19 through the various issues is an essential element to

20 doing the right thing.
21 And most importantly, you want to choose
22 an action that represents the best choice under the
23 circumstances. It seems self evident but again, at
24 the end of the day you want to know that you have
25 done that. And that I guess really gets to the
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1 second issue, which is you want to feel good about
2 what you have done. When you finish making a
3 decision, you want to feel as though you have had the
4 opportunity to make trade-offs between competing
5 considerations, complicated decisions, you got to
6 think them through, you have been able to think of
7 them, again, is this calm rational environment.
8 But ultimately one of the things, and
9 research in the area of general policy development
10 has demonstrated that people feel good, people don't
11 feel good when their decision making prerogative is
12 taken away. I mean, your policy makers, I don't know
13 that you necessarily want me as the decision analyst
14 or model developer to take away your prerogative to
15 make the policy. You would rather, and perhaps there
16 is some sort of optimization analysis, but rather, I
17 think that you might prefer to be able to make your
18 own decisions based on these various considerations.
19 Just from a very practical perspective,
20 again, in the general policy field, there have been
21 multiple examples in which optimization approaches or
22 prescriptive modeling, which I'll talk about a little
23 bit more in a second, have basically been the
24 examples of failure of the application of
25 quantitative methods for policy formation.
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1 And of course this is terribly important
2 to feel good; you want to have decisions that are
3 defensible to outside scrutiny.
4 Now let's move on to the issue of what are
5 the quantitative health policy models, and as Hal
6 mentioned, you're talking about decision models, and
7 I'm using the notion that quantitative health policy
8 models as being a fairly broad class of models.
9 We can talk about models in terms of what they are,
10 but we can also talk about them in terms of what they

11 do.
12 In terms of what they are, they have three
13 basic elements no matter what technique or approach
14 they use. The three elements are structure, inputs
15 and outputs, the structure being the critical
16 components of the decision. What are the elements of
17 the decision? They are the choices that need to be
18 made, the points of uncertainty and the valued
19 outcomes is the simplest classification. It
20 incorporates inputs, and ideally health policy models
21 are evidence based inputs, as opposed to randomly
22 selected numbers drawn from the air. And finally,
23 they produce quantitative outputs. For example,
24 survival, quality of life years, incremental cost
25 effectiveness ratios, and any other parameter that
.00175
1 the decision maker potentially might find useful.
2 So fundamentally, what health policy
3 models are as opposed to what they do, are
4 quantitative tools which are intended to influence
5 the agents of health policy, namely health policy
6 makers. So here is the link between the policy
7 formation and the quantitative modeling. Health
8 policy models are good if they in fact influence the
9 agents of health policy in a way that the health
10 policy makers feel good.
11 So how can health policy models help make
12 better health policy decisions? Now by the way, I
13 could have gone through some of the taxotomy of
14 decision models and simulation models and discrete
15 event models, and all kinds of models that can be
16 used, which I didn't think was the issue at hand. So
17 we can talk about that, if you like, but these again,
18 I think all of these apply to whatever models one
19 might choose in an effort to promote informed and
20 satisfactory decision making.
21 So how can health policy models make
22 better health policy decisions? And I think that
23 Dr. Sox mentioned one of them, one of the commonly
24 used approaches to using models for improving health
25 policy and that is to develop prescriptive models
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1 based on say expected utility. Now the notion here

2 is based in a theoretical foundation of Norman
3 Morganstern's axioms of utility theory, and again,
4 without going into those issues, you should read Alan
5 Garber's textbook, or chapter, or various chapters
6 and textbooks, and publications. But basically the
7 idea is that to the extent one subscribes to the
8 notion that the real world does or should conform to
9 the axioms of utility theory, prescriptive models can
10 lead policy makers to an optimum decision. Okay?
11 Now as I implied before, the problem with
12 prescriptive models is that there is a tendency to
13 see them as driving the decision as opposed to
14 guiding the decision, and so I raise the possibility,
15 I think an important possibility for you to consider,
16 and this is basically the theme of the whole
17 presentation, that policy models can be, quantitative
18 policy models can be extremely helpful even when they
19 are nonprescriptive, and I sometimes use the term
20 facilitative, because as mentioned earlier, models
21 can provide an explicit framework for supporting but
22 not necessarily prescribing policy.
23 And as I mentioned, you know, if you
24 develop a nonprescriptive model, ideally that should
25 be developed in such a way that it is consistent with
.00177
1 the prescriptive model and that can happen if you
2 develop the model with a utility structure as one of
3 the possible outcomes you can produce. So you can
4 use all of the insights that one might gain from
5 maximum expected utility decision theory but at the
6 same time for those of you who may not find that to
7 be a compelling way of making decisions, you also
8 have the opportunity to look at the other outcomes
9 that you care about like survival, five-year
10 survival, disability free survival, and so on.
11 So these nonprescriptive models are not
12 different models, they are basically a super set in
13 some sense, where the prescriptive models can be seen
14 as one kind of models that also are nonprescriptive
15 models. I don't know if I made that very clear, but
16 hopefully I did.
17 So what can models do? They can provide a
18 structure for visualizing complex issues. You can

19 only keep so many things in your head at one time, so
20 finally putting it down on paper is a nice touch. In
21 the case of the PET scanning issue, we were talking
22 about a variety of concerns, including the natural
23 history of disease, the efficacy of treatment, the
24 potential side effects of treatment, and so on. So
25 there were a number of issues to consider
.00178
1 simultaneously.
2 The models can provide a tool for
3 expressing how indirect evidence relates to
4 meaningful outcomes, and this again speaks to the
5 issue that Hal mentioned earlier. If you do not have
6 a clinical trial that says that, shows, a randomized
7 trial of PET scan, for example, in which you
8 randomize patients to receive PET scans or not
9 receive PET scans, and then follow them forward and
10 see how they do. I mean, that would be one
11 potentially ideal approach to obtaining the
12 information that you all want. And that hasn't been
13 done, and in the absence of that kind of evidence,
14 you need to create some indirect links that allow you
15 to make these inferences, and models are one approach
16 to do that.
17 In the case of a PET scanning model, we
18 found them an extremely useful way to guide our
19 literature search, and again, because through
20 sensitivity analysis you can identify those factors
21 that are most crucial in determining which would be a
22 preferred strategy, and you could make most of your
23 efforts, put most of your energy into coming up with
24 the best estimates of those factors.
25 And finally, and I think this is relevant
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1 here, it becomes a dynamic document, in general terms
2 a document that serves as a repository of best
3 evidence and can continue to be relevant as new data
4 is collected. I suppose we could call this the full
5 long-term employment for our center slide, because
6 basically the notion here is that data will hopefully
7 improve. There's going to be new tests, there's
8 going to be new information about the epidemiology of
9 disease, there are going to be new treatments. And

10 as all of these unfold, to the extent that the model
11 that we developed was developed with these general
12 issues in mind, you can come back and use it again.
13 And of course, that was one of the
14 reasons, as I mentioned, that we even included the
15 possibility, for example, that a new treatment might
16 actually make people, if people had a side effect
17 from the treatment, they might actually have their
18 dementia accelerate. That wasn't anything that we
19 had evidence for, but we did that with the notion
20 that somewhere down the line, there might be such a
21 treatment.
22 And again, you can get all of these
23 wonderful benefits without having the model
24 prescribing the policy. Now, before I get off the
25 issue about policy models per se, I'm going to give
.00180
1 you a taxonomy that it's based on how policy models
2 fit into the policy making process, which is
3 analysis, formation and implementation.
4 I think what most of what we are all
5 familiar in looking at quantitative models in
6 clinical medicine are what we would call in this
7 taxonomy the freestanding model. That's the kind of
8 thing that we all do as academics, and we say okay,
9 we're going to do the reference analysis based on
10 what we're told to do by experts in the field, we're
11 going to publish that, you know, we're going to use
12 the societal perspective, we're going to use quality,
13 all that sort of stuff. We publish it, we hope that
14 it's going to gain purchase in the community by
15 virtue of its wonderful writing and its wisdom.
16 So hopefully that influences policy but
17 generally indirectly, maybe not at all.
18 Now the model that we're talking about,
19 that we've talked about today, which is the PET
20 model, was I would like to think of as a member of
21 this class of facilitative models, something where
22 you had an opportunity to use the model, to question
23 it. We could go back. We had a lot of interactions
24 with Dr. Zarin and others at CMS that allowed us to
25 make modifications to the model. And the idea of a
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1 facilitative model then is it's developed
2 specifically with a policy making role in mind.
3 And then finally, sort of the holy grail
4 for anyone who wants to have quantitative modeling
5 applied to real world applications, it would be the
6 embedded model, and I sometimes like to think that
7 the work we've been doing in stroke is ultimately
8 leading to this holy grail model in which you develop
9 the model not only to better understand the evidence
10 but also as a mechanism for promoting practice
11 improvement, and we can go into that subject, but
12 that's not what we're here for. I just wanted to
13 mention that because that's I think the ideal.
14 But again, all without prescribing a
15 policy. One can use maximum expected utility notions
16 in order to help understand whether you've gained
17 insights or not for a certain model, but that's not
18 the only thing you can gain.
19 Some caveats, and some of these were
20 mentioned earlier. In turning to the lessons of
21 general public policy modeling such as economic
22 modeling, weather modeling and so on, these concerns
23 that you have raised here are concerns that are
24 raised in all of these areas. For example,
25 assumptions can drive conclusions. I could think of
.00182
1 examples, but I won't go into, time won't allow me to
2 go too much more into the PET scan issue and perhaps
3 we shouldn't here, but assumptions certainly can
4 drive conclusions and people worry about that.
5 Competing models may conflict. In fact,
6 Bob, the notion that competing models may conflict is
7 a concern, but it's also seen in some ways as being
8 positive, that one should not disregard when models
9 compete. And when I teach a course in which my
10 students evaluate decision and cost effectiveness
11 models, one of the potential jobs that they have is
12 to find competing conflicting models and try to
13 explain why they are different. And you can learn a
14 tremendous amount from identifying the differences
15 and the reason for the differences.
16 Complex models are difficult to
17 understand, again, a point just made, and very

18 legitimate, and that speaks to the issue that models
19 that are more complicated are not necessarily better.
20 Sometimes complicated models are just complicated.
21 And there is a notion here that I like to refer to
22 which again, I learned from Larry Phillips, is this
23 notion of the requisite model, and the requisite
24 model is a model which is sufficient in form and
25 function to address the problem at hand without being
.00183
1 more complex than necessary, and you know that you
2 have a requisite model because the people you're
3 working with, your clients, your policy makers, they
4 do not have a sense of disquiet that the model is
5 failing to address some fundamental concern that they
6 have, so that I guess is the technical definition of
7 a requisite model.
8 Insights may not be insights, they may be
9 bugs. And I think that all of these together
10 basically speak to the issue that when you work with
11 models, you're never going to be able to get away
12 from haunting concerns about validity, which again,
13 reinforces the notion that you should not be using
14 models. I would not recommend that you use models in
15 a very automated way in an optimization mode
16 primarily, but rather in a facilitative mode, because
17 you should always be constantly concerned about
18 validity and the degree to which insights may
19 actually represent errors.
20 Okay. So finally, getting to where the
21 rubber meets the road for you all, my recommendations
22 for MCAC, this really is daunting, but I will go on.
23 No when to commission a quantitative model, that's an
24 important concern. As mentioned earlier, when there
25 is no direct evidence, that's certainly one of the
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1 areas where modeling is something you want to do.
2 When there are complex competing issues
3 and it's important to visualize them graphically,
4 models provide you a graphical way of doing that.
5 And third, an issue of ongoing interest.
6 Again, as in the area of PET scanning, this is an
7 area you are going to be interested in for a long
8 time, you have this model, you own it now, go use it.

9 You paid for it.
10 You have to have basic expectations for a
11 model. I know that you're all aware of this, but
12 some of the basic expectations are involvement of
13 impartial experts to assure that the model reflects
14 the fundamentals of the problem at hand. Again, at
15 an early point in the PET scanning model, we engaged
16 clinicians and said are we capturing all of the
17 outcomes that people care about, which spoke to the
18 issue of whether all the health states were being
19 correctly addressed in the model. When we were
20 concerned about issues having to do with, for
21 example, what was the progression rate of dementia
22 among individuals without AD and we had a lack of
23 evidence in that area, we were able to sit down and
24 work with these experts and they helped us at a very
25 early point in structuring the analysis, and also
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1 structuring the model, and also structuring the
2 analysis that went into developing the inputs into
3 the model, which is an equally important problem to
4 developing the physical structure of the model.
5 Attention to extant models. In this case,
6 there were at least two models out there that were
7 published that we specifically sought out and spoke
8 with the individuals who were responsible for those
9 models to see whether we understood them entirely and
10 whether our model either was consistent with that
11 model or whether we may need to make some
12 modifications, or if indeed the other model might
13 actually have some problems with it.
14 Avoidance of unnecessary complexity, I
15 spoke to that issue.
16 Ability to generate outputs that decisions
17 makers care about, again, qualities are great. I
18 like qualities in a lot of ways, they can be useful,
19 but not everybody loves qualities and we just have to
20 accept that.
21 Explicit accounting of assumptions. You
22 will see there's a table in the analysis in the
23 technical assessment, and most good analysis I think
24 will do that, will provide an explicit accounting of
25 assumptions, the assumptions that go into the

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1 structure of the model and the assumptions that go
2 into the estimation of the model, because in order to
3 make an analysis that you can do in a reasonable
4 amount of time and explain requires assumptions, and
5 you have to list the assumptions and you have to
6 describe what you understand those assumptions, what
7 the impact those assumptions might have on your
8 conclusions.
9 And then finally, and this could be a talk
10 in and of itself, the issue of formal validation is
11 in the case of the PET model, I will just tell you
12 what we did, is that we had an analyst who was
13 experienced in developing models sit down with the
14 code, with the model, and go through it line by line,
15 and see whether it made any sense and see whether
16 there were any bugs that they could identify.
17 We went through a process also of varying
18 each of the inputs over not only its plausible range
19 but its implausible range to see if we had some
20 counterintuitive results and with the notion that
21 nine times out of ten counterintuitive conclusions
22 are bugs. And there are other forms of validation
23 that can be done.
24 But ultimately, I think establishing
25 standards for what you expect of a model in these
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1 various areas is essential.
2 And then understanding how to use a model
3 is important. I think this is a good start, and I
4 think having a basic education program that's not
5 designed to teach everybody here how to do these
6 models, because if we taught you how to do them then
7 we wouldn't have anything to do, but rather to make
8 you educated consumers so you can feel comfortable
9 that you ask the right questions, that you understood
10 what the sensitivity analysis really was about. What
11 the heck was that two-way sensitivity analysis there,
12 you know.
13 And making sure that the contractor
14 understands the committee's decisional needs. We
15 worked through an intermediary, that is Dr. Zarin at
16 AHRQ, and that was a very useful experience, and we

17 also had several conversations with committee members
18 in to do this as well, so we don't go off onto some
19 path of developing a model that was inconsistent with
20 your need. Also, consulting an external model
21 expert. We were happy about it because it turned out
22 well for us, but getting an external modeler to
23 inform consumers, you're going to have additional
24 questions and you should have a direct advocate by
25 your side to help, and that was something that was
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1 done during the subcommittee meeting and again, since
2 the comments all worked out nicely, I have nothing
3 negative to say about that component of the process.
4 So to summarize, decision makers want to
5 do the right thing and want to feel good about their
6 decisions. Health policy models are quantitative
7 tools which are intended to influence the agents of
8 health policy, namely policy makers, and this is what
9 it's all about, making good policy. Policy models
10 need not be prescriptive, but certainly a
11 prescriptive model can be contained within a general
12 model that you use in a facilitative way.
13 And this kind of nonprescriptive model can
14 provide a framework for explicit credible defensible
15 definitions, all without usurping your prerogative as
16 decision makers, and after all, what do you guys get
17 paid for? If you give me the problem and you ask me
18 to do a model, and I optimize for you and I come back
19 and say well, the maximum expected utility solution
20 is, what the heck are you going to do? Not to
21 mention the fact that I might be wrong, by the way.
22 Only commission a model when it has the
23 potential to help, and the three issues that I raised
24 were sort of guides to that. And I would say that in
25 general, you know, if it's a controversial or
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1 interesting issue, even a simple model can be very
2 useful if there are three or four components. Just
3 laying out that model in and of itself can be a
4 useful exercise in addition to being informative for
5 everybody on the committee to understand how to use
6 this process most effectively.
7 So I'd say basically, use modeling often

8 but commission a model and the expense of
9 commissioning a model only when it's a big issue like
10 this and there is an ongoing interest.
11 Establish standards and be informed
12 consumers, and that's it. Thank you.
13 DR. SOX: Does anybody have any questions
14 for Dave before we open up the general discussion?
15 Thank you.
16 Well, we now have some time to discuss the
17 role of decision models in our deliberations. Our
18 interim recommendations started out without really
19 explicitly incorporating decision models into them.
20 Then we developed a sort of simple approach, a quasi
21 decision analysis approach for evaluating diagnostic
22 tests which got us through the first round of PET
23 scan discussions, and now we've gone to expected
24 value decision making to guide us. I guess the real
25 question before us is, are we going in the right
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1 direction? Has this been a good experience or are we
2 digging ourselves a hole, either in respect to making
3 poor policy recommendations or losing our credibility
4 because we're using a technique either
5 inappropriately or a technique that people simply
6 don't understand or want to be guided by.
7 So Alan, maybe if I could ask you to begin
8 the discussion, what do you have to say on the
9 specific question of the direction we're going and
10 also are there some issues that we should be paying
11 attention to that neither David nor I covered.
12 DR. GARBER: I think what we have seen
13 thus far, at least from my perspective, and I guess
14 I'm not purely objective or impartial on this
15 subject, is that there are many questions we could
16 not have answered if we had avoided the use of
17 models. And I think there could be no doubt, for
18 example in looking at the multiple indications for
19 PET scanning, that if we had said can you directly
20 demonstrate an improvement in health outcomes, we
21 would have just had to say across the board that's
22 just not possible with the existing evidence base.
23 So I think if we were to say you can't use
24 models, you can only use direct evidence, we would be

25 painting ourselves into the corner because people
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1 need to make clinical decisions and we would not be
2 able to reach affirmative decisions very often if
3 that had been our criterion, we would have to wait a
4 long time for trials to be done, and they might never
5 come.
6 So I hope that it's not controversial that
7 the general idea of using modeling is the right one.
8 But I actually also have to say that I think in
9 practice it has worked out pretty well thus far in
10 terms of highlighting what the key issues are where
11 the data are uncertain, where we could use more data,
12 where we can draw fairly firm conclusions, and I
13 think it's very hard to generalize and we will have
14 to deal with use of modeling on a case-by-case basis
15 going forward.
16 But I personally am very encouraged. I
17 think that David Matchar and his group did a very
18 nice job in this study on PET for Alzheimer's, but
19 the other contractors have also done very nice jobs
20 and I found these very informative analyses. And I
21 have to also say that even if I were to disagree with
22 some aspects of the analyses, maybe some of the
23 assumptions made, they were extremely useful
24 frameworks for focusing the discussions. So in that
25 sense, I think it has been very successful.
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1 DR. SOX: Perhaps you can address a
2 technical question that comes up a lot in my line of
3 work, and that's sensitivity analyses in which you
4 basically do a simulation in which instead of
5 assuming -- and you assume some sort of distribution
6 for the values of the various factors and then you
7 basically look at all of them at once by doing some
8 sorts of simulation process that gives you some idea
9 of the distribution of expected qualities or expected
10 value instead of point estimates, and also have a
11 chance to look to some degree at the interaction
12 between different variables.
13 How should we be approaching this problem
14 of sensitivity analysis so we don't over simplify it?
15 DR. GARBER: Well, Hal, I guess you're

16 asking should we routinely do probabilistic
17 sensitivity analyses where eery parameter varies
18 simultaneously, and you know, this is something that
19 I'm not sure we could do justice to in a brief time
20 today and I won't really attempt it except to make
21 the general observation that it entirely depends on
22 the individual study or the individual subject, what
23 kinds of data we have.
24 I think the guiding principle for every
25 study that's used to help us, I like David's use of
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1 the term nonprescriptive and I think that all of the
2 time we do nonprescriptive or we look for
3 nonprescriptive analyses, ones that will help us
4 reach a decision but that don't tell us what the
5 decision will be. But in any case, in each
6 situation, sensitivity analysis has to be suitable,
7 and what's a suitable sensitivity analysis depends on
8 the data and how many things are really uncertain.
9 Hal is alluding to a technique that's very
10 popular and has many advantages, but it's only
11 useful, it is only as good as the assumptions built
12 into that type of sensitivity analysis, and I think
13 again, we would have to look at that on a
14 case-by-case basis. It can be very helpful in some
15 circumstances.
16 DR. SOX: Let's see. Go ahead, Bob.
17 DR. BROOK: I would just add two comments.
18 One, it's foolish to think that the sensitivity
19 analysis in these decision models or any models are
20 not subjective and not always explicit. All of them
21 require a great deal of judgment by the people who
22 model them and how you fill in missing data even if
23 you do this with wide sensitivity bands, because even
24 that requires subjective judgment, and virtually all
25 of these, they do not turn out to be robust to all of
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1 the decisions that people are making.
2 That doesn't argue against using them. I
3 believe we should use them, but I believe the major
4 purpose of this should not be for this committee. I
5 believe that the major purpose of this should be to
6 help provide guidance to the industry of what are the

7 critical pieces of information that are missing in
8 order to make better decisions about what things
9 ought to be done or not done, and I would urge the
10 government to try to explore the use of these
11 techniques way up front in the process when these
12 technologies and devices are actually developed, so
13 that people would really understand what are going to
14 be the critical pieces of information that are going
15 to drive the modeling and the evidence, and they are
16 not always obvious without setting up these explicit
17 models.
18 So in response to David's question about
19 when to do these things, almost any technology that
20 is going to consume millions of dollars of money,
21 which I think would be the hope of almost any one of
22 the manufacturers in the room, if not tens of
23 millions of dollars or in the case of PET scan,
24 billions of dollars, there is a need up front to
25 determine what evidence is needed, and I think by
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1 setting up these models up front, they ought to do it
2 and we ought to encourage through our modeling just
3 what the -- one of the products out of this ought to
4 be what are the things, gee whiz, why did you miss
5 doing this ten years ago and then come to us and be
6 upset with us when we say that a specific technology
7 is not worth it. There needs to be some thinking up
8 front using these models, this kind of approach to
9 figure out what kind of information is really needed
10 in this new age to produce a positive response from
11 this committee. That's where this ought to be put.
12 For us to do it at the end and get into this usual
13 contentious process, yeah, we're going to have to do
14 it, but it's not very satisfactory.
15 DR. SOX: So based on David's model, the
16 folks who were interested in building PET scanners
17 might know the target sensitivity that they need to
18 reach in order to have it be useful.
19 DR. BROOK: Absolutely, or the subgroups,
20 or whatever, but I really don't believe that's what
21 David wanted to do when he talked about the user. I
22 don't know if there is something out of this work
23 that you have written a report for the companies that

24 make PET scanners, to say here is the critical pieces
25 of information you need to know to really prove that
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1 your stuff is useful in improving the health of
2 people with AD, or what are the critical questions,
3 the pieces of information you need to know, if any,
4 if the outcome of this modeling is until there is a
5 better drug or a drug that is both better and no more
6 side effects, which is what I think I heard, then
7 that's another story. But what I'm really asking is,
8 we ought to try to prepare useful constructive
9 reports for the industry to help them make better
10 decisions and collect better data, and that ought to
11 be one of the options for these models.
12 DR. MATCHAR: In this specific
13 circumstance, this was, this group or the
14 subcommittee was the recipient of this, but I think
15 historically manufacturers have not been interested
16 in that, and only recently are they starting to, but
17 I think that they are looking to it, and this is why
18 I find this whole enterprise very exciting, because I
19 think manufacturers are starting to look at groups
20 like this and say well, okay, if this is how you're
21 going to do it, we'll play that game, because they
22 know that if they can understand someone more
23 explicitly how you are going to be making your
24 decisions, they will engage in this activity and they
25 will start to develop models early on, and some of
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1 the many manufacturers have approached various
2 modelers and the Society for Medical Decision Making
3 has even toyed with the notion of having some sort of
4 consulting service to guide the manufacturers to
5 increase their use of these technologies. And there
6 are plenty of private consultants out there doing
7 this. But it is certainly something that needs to be
8 done very very early on rather than at the end, and I
9 agree 100 percent.
10 DR. SOX: Perhaps I could interject a
11 concern here. If decision models which operate on
12 imperfect data become the norm, are we going to find
13 ourselves dealing with more and more imperfect data
14 because the motivation to create higher quality data

15 won't be there?
16 DR. BROOK: Well, Hal, I can't take it to
17 devices, but flying over here I read a series of
18 controversial papers on depression drugs that are
19 newly developed now being tested against placebo and
20 not other drugs. Now again, to test against other
21 drugs, you have to do some sort of modeling, because
22 you have to relate it back, and what they show is
23 depending on the year and the study that things are
24 done, the cure rate for major depression vice placebo
25 varied from 3 percent to 29 percent.
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1 So in the purest sense of the word, you
2 know, everything has to have a health outcome and
3 everything has to be tested in a randomized trial.
4 We know that that's not going to happen, and I would
5 think that we don't run the risk of encouraging both
6 decision modeling and real data. And one of the
7 things that ought to come out of this is the balance
8 between the two.
9 Now, I'll add a third piece. I believe
10 that it's absolutely incumbent upon people to change
11 the willingness to give information so that we're
12 going to have to go through large observational
13 databases as well. For instance, I think it's
14 absolutely wrong for somebody to offer PET scanning
15 to anybody without first putting together, let's say
16 I have an entry point for PET scanning and I make a
17 decision to do it or not do it. If I'm going to do
18 that, I think the commitment for people who get that,
19 even though it may be paid out of their own pocket,
20 ought to be that you develop an absolute complete
21 database of the covariants up front, the decision
22 that was made about whether to give it or not, and
23 outcomes, and that that be pooled and not just be the
24 purview of one single group of investigators. And
25 that because I think in the modeling in general,
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1 somebody is going to have to have that resource. And
2 so I think these are the types of changes that we can
3 stimulate, because I don't think we us observational
4 data very well, we don't collect it very well, we
5 don't use modeling very well, and we certainly don't

6 have a balanced decision between randomized trials
7 and decision analysis very well.
8 And with the new IRB approvals, I am just
9 wondering what we will be able -- I mean, I am
10 seriously wondering what kind of randomized trials we
11 will be able to do given where the IRB process is now
12 going in many of the academic institutions.
13 DR. SOX: That's the other side of
14 discouraging randomized trials is maybe they are not
15 going to be feasible. Leslie?
16 DR. FRANCIS: I just want to say that
17 we're sort of roughly on the recommendatory, which is
18 a kind of soft prescription side of things in what we
19 do here, and as somebody who you know, sort of sits
20 here expected to play something like that role, when
21 I read a model, I have the meat hamburger theory of
22 models, you stick stuff in it, and the most important
23 thing is what you stick in it, and therefore -- and
24 then grind it up, and therefore, it's most helpful to
25 me when I read a model to get as much information as
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1 I can about the choices and the controversies that
2 were involved in the choices about what to stick in.
3 I mean, I thought I had a pretty good
4 sense of that from this model, but actually the one
5 that was hardest for me to swallow just reading it,
6 you know, before I came, was the no treat, I mean the
7 treat all assumption. So that's just a comment
8 about, as a consumer of a model who's going to have
9 to make certain judgments about what it can be used
10 for, the more information there is about those
11 up-front choices and what they are based on and how
12 hard or soft they are, the happier I am.
13 DR. SOX: Unfortunately, journal editors
14 in their desire to publish more with fewer extensive
15 pages often end up truncating the type of discussion
16 you're calling for.
17 DR. FRANCIS: Exactly, but when somebody
18 prepares a model that we buy, they don't have to meet
19 the journal editors editorial strictures.
20 DR. BROOK: You may need to talk to David
21 about this. I would think it would be useful for CMS
22 if we're going to use these things, to develop a web

23 based library of these models. I don't know who
24 maintains that and whether it's the Society for
25 Decision Making, but I really don't believe that the
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1 peer reviewed 12-page format of models is appropriate
2 at all, and I would believe that we probably
3 eventually will need to go on record that any one
4 such model that comes out of that, that the whole
5 explicit activity ought to be in some web based
6 preserve archive and that somebody needs to review
7 that to say that if David Matchar no longer was
8 interested in this subject, somebody else could pick
9 up what he did, understand it, and do exactly what
10 David said, which was to build on it with new data
11 and new evidence, without starting over again.
12 So how we catalog the programs, how we
13 make this user friendly, we just have never developed
14 that. So even if it's explicit on a web, it's
15 probably unlikely that any smart computer person will
16 be able to figure it out enough to actually redo it,
17 without spending hours with David's team to do it.
18 DR. SOX: But one thing we could do along
19 the same lines is to have a certain user friendly
20 interface with the computer so that any person could
21 go up and mess with the variables. Wade, I think
22 you're next.
23 DR. AUBRY: I just wanted to add a comment
24 that I thought we are on the right track and I would
25 like to see CMS and this committee further develop
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1 the models, but I would also like to share the
2 concern about potentially inhibiting the development
3 of direct evidence. I know in my experience with the
4 Blue Cross/Blue Shield TEC program, there were
5 numerous instances of reviewing an intervention for a
6 relatively common condition in which it would be
7 relatively easy in terms of generating patients to
8 study the intervention but it was not done, and the
9 quality of the evidence was low.
10 So I think the decision to proceed with a
11 model for evaluating a given topic should be on a
12 case-by-case basis and it should include not only the
13 issues that David referred to such as there's little

14 if any direct evidence and that a model could
15 potentially help, but also, there should be a
16 determination that it would be difficult to develop
17 the type of direct evidence that would be needed.
18 And there are examples in my own career
19 where I have looked at a topic, particularly in
20 diagnostic testing, in which a study could have been
21 done, and then I looked at it again ten years later,
22 and there still is little direct evidence. So I
23 think the committee and CMS should have a reasonable
24 high bar for direct evidence when that evidence could
25 be developed. If it's a very rare condition, that
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1 may be a different consideration, and we touched on
2 that a little bit at the last meeting with some, I
3 think there was some discussion about pediatric
4 cancer interventions for example. But I just wanted
5 to underscore that point.
6 DR. SOX: Sean, do you want to comment on
7 this issue of discouraging better forms of evidence
8 by using models that incorporate relatively imperfect
9 data. Maybe you'd like to say something after you
10 have a chance to reflect, or maybe you'd rather not
11 say anything at all.
12 (Laughter.)
13 DR. TUNIS: Maybe I'll do both of those
14 things, say something without saying anything.
15 (Laughter.)
16 No, I will sort of turn it into a
17 question, which is, you know, my assumption is that
18 built into the techniques of modeling is
19 consideration of the underlying evidence that goes
20 into the model and therefore, the output of the model
21 will naturally reflect, or the sensitivity analysis
22 in some way, the quality of the underlying evidence.
23 So I would presume that the mere fact of using
24 modeling as a component of decision making wouldn't
25 by itself, you know, undo the incentive to gather
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1 high quality direct evidence as an inherently more
2 reliable form of evidence. But, that's virtually a
3 question, but that reflects my own knowledge about
4 modeling but also the use of evidence in policy

5 making, so that we would continue to consider the
6 quality of the underlying evidence even if it were
7 incorporated into a model as part of the thinking
8 process.
9 DR. SOX: Of course the decision model can
10 tell you the parameters of the model for which you
11 require high quality evidence and on those, you may
12 not be able to make a coverage decision because, it
13 was not the case here, but there are some situations
14 where a critical parameter makes you unable to make
15 the call because the range of reasonable values for a
16 probability or utility, you know, the preferred
17 option changes so it becomes a close call without
18 more precise knowledge of what's good data.
19 DR. BROOK: One of the questions, Hal,
20 that I thought would be interesting to look at would
21 be, you know, the Duke cardiovascular database
22 produced similar results to the randomized trials
23 about when to do bypass surgery, very similar. And
24 it would be very interesting if we could develop a
25 body of information about when this kind of work, and
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1 when good modeling and this kind of work, you know,
2 the interface, the balance between that and
3 randomized trials. Nobody has done that, but when
4 those studies have been published, you know, how do
5 we use them, because we're going to have to make some
6 decision. And if we only had that kind of data on a
7 controversial topic like that, would we approve it?
8 I mean, if all we had was a good observational
9 database about left mane disease and medical or
10 whatever therapy, would we approve it?
11 DR. SOX: Barbara.
12 DR. MCNEIL: I have a slightly more simple
13 minded suggestion than Bob's, but first a comment.
14 Wade, I actually looked up the Blue Cross series of
15 evaluations for the year 2000, and tallied the
16 percent of them that we couldn't make a decision on
17 because of inadequate database, and it was 40
18 percent, so it was quite large for that year.
19 But my suggestion, going on what everyone
20 said, is the following, just a summary. It seems to
21 me that Bob Brook has said that these models are

22 useful for identifying up-front variables on which
23 the decision is key. And then we said earlier that
24 the result of this model was also useful for
25 identifying prospective research studies, and there
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1 is some relationship between the two of those. And
2 the third thing that we said was that a lot hangs on
3 the Y axis on the utility scale whether it's a simple
4 expected value, or even if we get to cost
5 effectiveness, that utility scale means a lot.
6 And I have been impressed listening to the
7 comments around the table, and I wish Randel were
8 here. Would it ever be possible, and maybe you've
9 thought about this, Sean, for CMS to have a
10 conference in which we, a very small conference in
11 which we invite leading device manufacturers and pull
12 out some of the examples that we have had in terms of
13 raw data and modeling data. And say for example,
14 let's look at the breast cancer one on PET, and
15 before we ever did a study, we would have known that
16 that wasn't going to make it, just because of the
17 implications of false negatives. And now let's look
18 at the model of PET for Alzheimer's and what might
19 have been predicted beforehand and what implications
20 those models show for future studies. And basically
21 have a little bit of a tutorial about how industry
22 should be thinking prospectively about how to
23 maximize the chance that the good things will get
24 properly evaluated and move through the system.
25 I think there really is an educational
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1 gap, because this does get pretty technical and it
2 has never really been put together in an integrated
3 user friendly fashion, and I think maybe we could do
4 that.
5 DR. SOX: If we could agree, if industry
6 developed decision models to guide their evaluation
7 process, and we did this in a more cooperative
8 fashion with the clinical community, we could make an
9 advance, I think.
10 DR. McNEIL: I was suggesting to help them
11 come to their conclusion, we would give them some
12 examples from our portfolio.

13 DR. SOX: Yours would be a first step, and
14 not in the context of a specific issue where it's all
15 charged up and nobody wants to concede an inch.
16 DR. MCNEIL: Right.
17 DR. SOX: Alan.
18 DR. GARBER: Well, Hal, I want to get back
19 to your question about whether the use of models
20 would dissuade various parties from carrying out
21 trials basically, and when it comes to diagnostic
22 tests, I am not terribly concerned about that issue,
23 since right now there aren't that many randomized
24 trials done, it's a fairly rare event to have
25 randomized trials that look at final health outcomes.
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1 So there is not really anything to discourage at this
2 point. And I wish I had a view of the future that
3 was so rosy that I thought there would be a lot of
4 these trials coming forth that we might somehow
5 discourage, but I don't think that's realistic.
6 I do think that it's very important for
7 the panels, though, to continue to do what they have
8 done so far in looking at the data and being pretty
9 clear about looking at the assumptions and whether
10 good data support these assumptions. In the context
11 of the PET for AD, they look carefully at whether
12 there is enough data to suggest it was sensitive and
13 specific, what the basis for the accuracy result was
14 and so on. And we depend very heavily on our panels
15 to be consistent in application of evidence criteria
16 for the components of the models, and that's a lot of
17 what we heard about.
18 And as long as they continue to apply
19 those criteria, the people who produce these
20 technologies will indeed have an incentive to do
21 appropriate studies to look at these aspects like
22 sensitivity, specificity and whether treatment works
23 given the diagnosis.
24 DR. SOX: John.
25 DR. FERGUSON: Just a question. Does the
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1 FDA accept models from the industry or from anybody?
2 DR. HOLOHAN: Maybe I can answer that in
3 the absence of an FDA official here, that the FDA

4 rules are in the Code of Federal Regulations, and the
5 CFR states on the basis of well controlled trials,
6 and that's been held by courts to be more than one
7 trial. Controlled doesn't necessarily mean
8 randomized blinded trials, but no, you have to
9 provide substantive evidence of safety and
10 effectiveness.
11 DR. TUNIS: The only other comment on that
12 is that the FDA rules for adding a second clinical
13 indication to an already approved labeled indication,
14 in other words, changing an off label use to a label
15 claim, can be supported in some cases by a
16 meta-analysis of small trials without doing what
17 would qualify as a fully powered pivotal trial, but
18 that has only occurred in a few cases and I am not
19 aware of any example where a decision model has
20 supported even a second indication.
21 DR. HOLOHAN: To further complicate it,
22 there's the issue of surrogate also. The FDA does
23 accept certain surrogate influence as evidence of
24 effectiveness of antihypertensive drugs, lipid
25 lowering agents.
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1 DR. SOX: Bob.
2 DR. BROOK: But we're in a whole different
3 game here, and that game is the same game. I mean,
4 if somebody asks us to evaluate the effectiveness of
5 a neurological workup for AD, should, is the
6 technology so simple if it was applied by an
7 internist or family practitioner that you don't need
8 a neurologist at all, then we shouldn't pay for it.
9 Or what's the frequency of visits that a doctor ought
10 to be paid for for hypertension, or do you need any
11 visits with e-mail?
12 Now, all we have done is throw this back
13 to recapitate physicians and then let them figure out
14 what to do and worry about them being sued, but we
15 have no evidence on any of this kind of stuff. So
16 we're now in this whole issue of devices, visits,
17 professional time. We have no evidence, nor do we
18 randomize before we decide that an HMO can cut the
19 time with a patient from 15 minutes to 12 minutes, we
20 don't randomize that and look at outcomes.

21 So, we have a mess, and I just wonder
22 whether or not the stuff that Barbara was talking
23 about, if we change the way we operated and said that
24 down the road this committee is likely to require
25 randomized trial data here, modeling here, this was
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1 based up front on getting together with the
2 manufacturers of a product very early on in the
3 developmental phase so that one could actually try to
4 be smart enough to model out this, and say look,
5 here's what the key data are really going to be, and
6 then this committee could up front, or one of the
7 subcommittees say, it's likely that we will probably
8 want randomized trial data here, or model data here,
9 that would be extraordinarily helpful.
10 I mean, they are in an industry -- I mean,
11 this is not the tobacco companies trying to kill
12 people. This is a group of people that are trying to
13 make people better. And you know, the faster that
14 happens, the better off we will all be. So the
15 question is, can we change this process, are they
16 willing to do it, but I think the government ought to
17 explore that.
18 DR. SOX: Further comments or questions?
19 Yes, Leslie.
20 DR. FRANCIS: These models always get
21 constructed as against existing practice in certain
22 ways, so that suppose for example, PET had been on
23 the horizon, I mean had been adopted 30 years ago,
24 and the question were clinical evaluation. So the
25 question was, is clinical evaluation, does it change
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1 the decision tree, you know. In a way I would have
2 wanted to know that, but I didn't know that.
3 DR. SOX: Compared with what?
4 DR. FRANCIS: With PET. I mean one of the
5 things is you always do a model against a background,
6 and the more we know about, one of the things that's
7 just a mess here is that there's all this stuff that
8 everybody just does that nobody has ever looked at,
9 but the more we know about what the background is,
10 the better we can decide how to use the model.
11 DR. SOX: Well, I think I will bring this

12 discussion to a close by suggesting to Sean that we
13 have uncovered a lot of opportunities and potential
14 problems as a result of having had a very successful
15 discussion about a technology based almost entirely
16 on decision modeling and imperfect data, and that we
17 do need to continue to talk about this off-line, and
18 we have had a number of good suggestions about
19 developing our ideas, starting to talk to industry
20 about it, developing databases of decision models,
21 and trying to encourage a lot of very early stage
22 planning of both evaluation and in fact what you
23 ought to try to build, and we need to continue that
24 process. And I guess on behalf of the committee, I
25 will ask you to figure out a way to get some of us at
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1 least together to start thinking about that.
2 DR. TUNIS: We will certainly do that and
3 follow up on suggestions that Barbara, you raised,
4 and I think Bob also, to get more fleshed out some of
5 the ideas you had, including potentially working
6 together with AHRQ to have a small conference to
7 follow up and explore this in a little more depth.
8 I'm volunteering AHRQ because they have more money
9 than we do.
10 (Laughter.)
11 So we will certainly follow, take that as
12 a directive from the executive committee and follow
13 up on that.
14 DR. SOX: Now would be an opportunity for
15 anybody who would like to step up to the microphone
16 and comment on this particular topic. We would like
17 advice from some of you who are in the audience.
18 Yes, if you would identify yourself and where you're
19 from.
20 DR. HERNANDEZ: I'm John Hernandez. I'm a
21 health economist and health outcomes researcher at
22 Boston Scientific, a medical device manufacturer, and
23 I appreciate the opportunity to follow the
24 committee's discussion on decision analytic modeling
25 and the opportunity to share my thoughts with you on
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1 this issue.
2 In general the medical technology industry

3 is strongly supportive of using appropriate
4 analytical and empirical modeling to support decision
5 making in health policy, and it's important that
6 these tools be used in a manner that insures
7 transparency and accountability in the Medicare
8 coverage process. And if used appropriately, we do
9 believe that decision analytic modeling offers the
10 potential to support policy makers in understanding,
11 analyzing and making decisions regarding these
12 healthcare policy problems.
13 There are a number of examples where
14 decision analytic models have been used successfully
15 to support complex decision making. In World War II
16 at military decision making, at Rand, and in the
17 United States Government at the Pentagon, and in
18 other situations. It is also be being broadly used
19 in the business community to make decisions as well.
20 More recently, a growing body of research
21 has been published demonstrating application of these
22 techniques to analyze healthcare decisions. And that
23 said, there has been limited study to date of the
24 applicability and usefulness that decision analytic
25 modeling techniques directly and formally to assist
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1 healthcare policy decision making. The increased
2 adoption of structured methods and processes for
3 decision making in Medicare has been underway for
4 quite some time and we applaud this trend as it
5 provides a level of transparency and accountability
6 that is rightfully demanded by the program's
7 recipients and participants.
8 As you begin contemplating the appropriate
9 role for decision analytic modeling in the Medicare
10 coverage process, we ask that you keep in mind
11 several issues, some of which will echo the points
12 already made by Bob Brook, David Matchar and in the
13 recent discussion, and we actually note that several
14 recent reviews have concluded that decision analytic
15 modeling is likely to be used and most usefully
16 integrated into the policy process, if it is used
17 simply as one form of input into the decision making
18 process, and that there are dangers to utilizing such
19 models if they are adopted in a manner that's overly

20 rigid or mechanistic, as they will be viewed
21 rightfully and as mentioned by David Matchar as
22 usurping the role of decision makers.
23 One researcher, and this was mentioned
24 before, who has investigated the utility of decision
25 analytic modeling in the consensus panel development
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1 process, David Powker, has identified a number of
2 problems that can limit the utility of formal
3 modeling in conjunction with these panels. In fact,
4 a major conclusion was that panels almost uniformly
5 have avoided specific mention of decision analytic
6 concepts in their recommendations.
7 And the role of decision analytic modeling
8 in the panel recommendations discussed today is
9 relatively unusual. Specifically, the medical, I as
10 a representative of the medical technology industry
11 recommend that if decision analytic models are going
12 to be used formally in the MCAC process that you pay
13 some attention to the processes and to the methods
14 that is going to be employed by the MCAC and that
15 specifically formal recommendations should be
16 developed in the MCAC recommendations for evaluating
17 effectiveness. And specifically, I believe this
18 should be discussed in the suggestions for panel
19 operations and in a separate section under issues on
20 methodology.
21 We also would very much like to engage
22 with CMS and perhaps AHRQ to discuss this informally
23 as well.
24 I would like to point out that results,
25 and this has been discussed I believe already, that
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1 decision analytic modeling can be highly dependent on
2 a large variety of methodological and technical
3 factors. I think that there is a large literature
4 showing that cost effectiveness analyses can have up
5 to 20-fold differences in results due to technical
6 decisions made by model constructors and similarly in
7 the utility analysis world, Eric Nord and others have
8 shown the impact of methodological differences in
9 results on measuring utilities.
10 Other issues that have been mentioned that

11 can impact outcomes have to do with the subgroups
12 chosen, time horizons used in these models, decision
13 options, consideration of costs, and many other
14 factors, and these should be specifically considered
15 before being broadly used in the MCAC process.
16 Thank you very much for your time.
17 DR. SOX: Thank you very much. Anybody
18 else that would like to step forward? Yes, please
19 identify yourself and where you're from.
20 MS. MARX: I'm Sandy Marx, with the
21 American Medical Association. I thought this was a
22 very interesting discussion and I was going to get up
23 just to repeat something that the previous speaker
24 mentioned about integrating the use of decision
25 models into your recommendations for evaluating
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1 effectiveness, so that there is some comprehensive
2 tool that people have when they're looking to pursue
3 a coverage decision that identifies all the possible
4 ways you're going to look at the available evidence.
5 And I think that document also gets into a
6 sort of hierarchy of evidence, which sort of
7 addresses the problem you raised about are we going
8 to discourage doing randomized controlled trials.
9 Clearly anyone who wants to see their new product
10 covered is going to realize that if they have good
11 evidence from multiple randomized controlled trials
12 they are going to have a greater likelihood of
13 getting a positive coverage decision than if they
14 just have expert opinion. And somewhere in between
15 those two extremes maybe, or two ends, is going to be
16 this decision model process that can pull together
17 the observational study. So to integrate that into
18 the rest of the work that you've done I think would
19 be helpful, because there are a lot more people
20 interested in what you are doing and how you do it
21 than just the people in this room who have heard this
22 discussion.
23 DR. SOX: Thank you. We're now going to
24 hear from Sean about changes to, in the voting
25 process, and I guess our responsibilities. Is that
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1 right, Sean?

2 DR. TUNIS: Well, actually just to get
3 some input from you on some ideas about how we might
4 reformulate some of the questions. And I promise, we
5 will be done by five after three at the latest,
6 somewhere around then, and actually, Jeff Kiang is
7 going to come back and wants to talk to folks
8 briefly, and he is finishing up a talk at three, so
9 he will be back a few minutes after that.
10 So this is really again, to get some
11 feedback from you all on some internal discussions we
12 have been having about possibility of potentially
13 improving the way we frame the questions in our panel
14 meetings to get a full, the full range of views
15 express that are relative to coverage decisions. Our
16 observation is that our current voting questions may
17 not give a full opportunity to address all the issues
18 that are relevant to coverage decisions. We do
19 sometimes find ourselves, you know, after MCAC
20 meetings as we're trying to formulate policy, wishing
21 we had a chance to go back to the panel and ask some
22 additional questions, so what we are talking about
23 here is whether we can modify the existing questions
24 or add some new questions that would get some more
25 information.
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1 The issue is whether the current questions
2 are too narrow, particularly a yes-no question on the
3 adequacy of evidence, it's obviously a critical
4 question, I'm not suggesting that we eliminate that
5 question, but it does provide sometimes a framework
6 that has in some cases been interpreted as too
7 narrow. Obviously this is fundamental to the
8 guidelines on evaluating effectiveness, so again,
9 this is not intending to replace that, but trying to
10 see if there is some way to open it up and maintain
11 the value of that framework as well.
12 But there are other perspectives,
13 opinions, observations about a technology, the
14 condition that the technology is directed towards,
15 alternative technologies that are important issues
16 and may be relevant to have the panel discuss in this
17 public forum.
18 One thing I just want to point out is that

19 the MCAC, as you know, is one of the only existing
20 public forum dedicated to discussion of complex
21 issues raised by new medical technology. There is
22 the Blue Cross/Blue Shield has a technology forum and
23 I'm not aware that that's actually a public forum.
24 The NIH consensus forum is a forum in which
25 technology issues are addressed, but really for
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1 Medicare being the largest single payer, when it
2 addresses a technology, it has ramifications that are
3 much broader than just the Medicare program, and we
4 may not be fully taking advantage of our opportunity
5 to get into the more complex controversial issues
6 raised by medical technology just focusing on
7 adequacy of evidence.
8 So anyway, how can we make best use of
9 this opportunity given these issues? So, the first
10 notion is whether in addition to or instead of the
11 yes-no on is the evidence sufficient, is it possible
12 to, would it make sense to ask a question of how
13 would you rate the overall quality of evidence,
14 possibly dividing it into simple categories like
15 good, fair or poor, rather than the simple yes-no of
16 it is sufficient or it isn't sufficient. In other
17 words, that the panel would come to some assessment,
18 sort of a graded assessment, if you will, of the
19 quality of the evidence. I think this issue has been
20 raised and possibly discussed before but we're
21 raising it again for discussion.
22 And then some additional questions, some
23 of which by the way were reflected in those
24 additional questions that were directed to the
25 imaging panel related to PET for Alzheimer's was the
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1 beginnings of our thinking on this. Magnitude of
2 effect, this is already part of the interim
3 guidelines, so this is just, this would not be a
4 change. We're talking about the relative benefit,
5 the size of the effect over existing alternatives,
6 less effective, more effective, equally effective, I
7 think there is seven categories in the existing
8 interim guidelines.
9 But new questions would be what's the

10 clinical impact of the technology, in other words
11 talking about what's the current state of practice
12 absent the technology, what potential harms might the
13 technology pose if it were broadly disseminated, are
14 there specific patient selection criteria that need
15 to be considered more narrow than should the thing be
16 covered or not covered broadly, so to try to get some
17 more into some of these issues.
18 The research consequences, a little bit of
19 this has been raised today in the context of the
20 modeling discussion, but would coverage and broad
21 dissemination encourage or discourage research, or
22 improve or not improve the existing medical evidence.
23 In other words, looking at the potential impact of
24 coverage on what sort of research might be conducted,
25 identifying what additional research should be
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1 performed to make the best conclusions even if we do
2 offer coverage, you know, being more specific, trying
3 to get the panel to be more specific about what the
4 follow-on research should be, and also talking about
5 what barriers might exist to performing the research,
6 including burden on industry, the cost, ethical
7 difficulties in potentially doing studies, and
8 possibly methodologic challenges of doing follow-on
9 studies.
10 And then, we don't often talk about
11 criteria such as what sort of staffing and facility
12 criteria should be considered in the use of the
13 technology. We do this for transplant facilities
14 routinely in the Medicare program of having certain
15 minimum outcomes per year and certain numbers of
16 transplants, but we don't talk about certain facility
17 criteria for other technologies, and this issue
18 doesn't often get raised.
19 And then questions about whether there are
20 certain characteristics of a device that should be
21 considered in terms of when we evaluate a technology.
22 For example, the whole issue around PET scanners of
23 gamma scanners versus full ring PET, we often don't
24 get into details within categories of technology.
25 In terms of the process for formulating
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1 these questions, these potential additional
2 questions, the idea would be that we would try to
3 come up with the questions prior to the meeting based
4 on some standard formula, in other words, identifying
5 the content area of the questions as we have done
6 here, but they would be customized to the particular
7 issue, and we develope the questions in consultation
8 with the requester, advocates, industry, consumers;
9 in other words, this would be part of the open public
10 process of actually getting input on what questions
11 should be posed to the panel in addition to the
12 questions evaluating the evidence.
13 So, we would like to hear a little bit of
14 discussion for the next five or ten minutes, this
15 won't be the end of the discussion, but what are the
16 pros and cons of modifying the existing key
17 questions, just yes-no on the sufficiency of the
18 evidence; if the answer is yes, what categories of
19 questions should we be looking into. Any suggestions
20 on the process for developing the questions, how we
21 can engage MCAC in this discussion, and any other
22 thoughts on this topic.
23 So I'll sit down and take your comments,
24 but again, the idea is trying to figure out how,
25 given that it's difficult to get all your brains in
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1 the room at the same time, we want to take maximum
2 advantage, plus, we pay you I think $400 a day and we
3 want to make sure we get our money's worth for the
4 public.
5 (Laughter.)
6 DR. SOX: Leslie.
7 DR. FRANCIS: I mean, you guys shape us in
8 a way, so if you want more information, it's entirely
9 reasonable to ask for it. The only thing that I must
10 say that I found frustrating several times, and it
11 was illustrated again today, is if the question gets
12 changed in some way, that people don't feel that they
13 had an adequate opportunity to answer it. What
14 happens is that things get shoved over into process
15 questions and rather than substance questions, and we
16 want to try to avoid that as much as possible. So if
17 questions get added or if people realize that

18 questions need to be changed, it should be done with
19 adequate time for airing these discussions.
20 DR. SOX: Are you talking about the
21 questions that sort of form the basis of the charge
22 to the EPC that writes the evidence report, is that
23 what you're talking about?
24 DR. TUNIS: No, this is questions to the
25 MCAC, to you know, to guide at least part of the
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1 discussion, and again, sort of with the intention of
2 trying to systematically raise all of the critical
3 issues that are going to be pertinent to making
4 coverage decisions. So, I mean, just as an example,
5 we don't often systematically talk about what's the
6 standard of care and the adequacy of the standard
7 when discussing a new technology. I mean, there are
8 a whole set of issues that sort may sort of
9 haphazardly come up in conversation, but we haven't
10 traditionally made the effort of trying to identify
11 those in advance and make sure that they get
12 addressed in the conversation.
13 DR. SOX: Alan.
14 DR. GARBER: Well, Sean, I think the set
15 of questions you raise is quite interesting and there
16 are many directions you could go with this, and
17 rather than address all the possibilities, let me
18 just give you my two cents worth.
19 First of all, I think it is very important
20 for MCAC as a process to be successful to be fairly
21 consistent with at least a core of questions, and I
22 think we have that start right now. So I would first
23 suggest that anything we do should be considered
24 add-ons rather than substitutes for what we have
25 already developed.
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1 And on the question of add-ons, some of
2 the things that you are raising, first of all, will
3 only be interesting in particular cases and would not
4 be very interesting to do in general. And secondly,
5 some of these may be far more difficult than we
6 recognize today. Like an evaluation of standard
7 practice. You can imagine how difficult it is just
8 to define standard practice, and then to try to find

9 a body of literature that would enable you to draw
10 fairly firm conclusions about the state of evidence
11 backing up current practice, I can certainly imagine
12 that that would be something worth pursuing in some
13 instances but I would imagine that's going to be
14 rare.
15 So, I think that if you're asking should
16 we occasionally include some of these additional
17 questions, the answer is probably yes. I mean, I
18 think as a member of MCAC I would be happy to be
19 involved in a discussion of these added topics, but
20 it has to be your call about when it's important and
21 relevant. And you have to recognize that you have to
22 add on questions very judiciously because we could
23 eat up all our time on things that may not be all
24 that central to your coverage decision.
25 DR. SOX: Just to challenge you a little
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1 bit on that, Alan, it strikes me that we don't do a
2 very good job here of putting the candidate
3 technology into the context of total care for a
4 problem. To give you an example, the mercury
5 sphygomanometer, we could evaluate that and find that
6 it's accurate and that it adds lots of quality
7 adjusted life years, but in so doing, if we didn't
8 identify the problem with compliance with medication,
9 failure to screen, failure to do cardiac risk
10 reduction assessment in all patients that are
11 hypertensive, those may be the things that are
12 barriers that are getting in the way of successfully
13 dealing with the problem of hypertension and its
14 consequences.
15 And I have a feeling that when we respond
16 to a coverage request that we're going kind of doing
17 this, looking at it through a pea shooter, and that
18 we really need to step back as part of our
19 evaluation, put it into a larger context, not as the
20 people that are advocating for a technology that may
21 be fairly marginal, but how does it fit into the big
22 picture of how good a job we're doing and what the
23 rate limiting factors are in succeeding.
24 DR. GARBER: Well, the issue here in an
25 ideal world where we had, or I should say imaginary

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1 world anymore, where CMS had unlimited resources and
2 time, Hal, I think the thing that you're proposing,
3 to do a very comprehensive review of all the
4 treatment conditions and the basis for all treatment
5 and condition would be something you would want to
6 do. But we're talking about tradeoffs here and what
7 CMS really needs to know to make a coverage decision.
8 And that's why I'm saying you have to be judicious.
9 And what you're talking about doing for
10 hypertension, we would be spending 10 percent of our
11 time potentially on the topic of ambulatory blood
12 pressure monitoring, and 90 percent on the treatment
13 of hypertension. Now that's an exercise that has
14 considerable value, but it also has considerable
15 costs, and I think there are going to be times when
16 that's going to make a difference to the ultimate
17 coverage decisions, and times when it isn't, and I
18 think Sean and the CMS staff need to be very careful
19 when making those choices, deciding when to do the
20 big big study. But we've seen how much discussion we
21 generate over fairly narrow questions and when you
22 throw in about 10 times as many considerations, and
23 that's no exaggeration on the topic you're talking
24 about, you have to figure, are we really going to be
25 able to do an adequate job on any of it.
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1 DR. SOX: Well, there is probably some
2 middle ground between my quickly listing a few topics
3 and doing a very expensive analysis that's already
4 been done out there in several existing articles.
5 But anyway, there's probably some middle ground.
6 Other comments? Wade.
7 DR. AUBRY: I was just going to say that I
8 think there are two categories of questions. One is
9 being responsive to the coverage request. The
10 coverage request comes in, there's a process that has
11 been published in the Federal Register as to how the
12 Medicare coverage process works, and so one question
13 that needs to be addressed has to be responsive to
14 the requester.
15 The second part of it, however, is to
16 develop other questions that make sense to evaluate

17 in the context of looking at that subject, and it
18 seems to me that that should include input from other
19 groups, including the committee itself, perhaps the
20 Medicare carrier, medical directors, perhaps
21 interested specialty societies, and so a broader call
22 for key questions may be appropriate. But I share
23 Alan Garber's concern that that may yield sort of an
24 unwieldy number of questions, and that would need to
25 be sort of narrowed down to the key areas by CMS
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1 staff.
2 But I think that the committee in order to
3 adequately address a topic should do more than just
4 respond to the coverage request if they're going to
5 look at a topic.
6 DR. SOX: Bob.
7 DR. BROOK: I'm a little confused and I
8 think at some point we may need to revisit the entire
9 process. Let me tell you what I'm confused about.
10 Today we said we weren't going to use this procedure.
11 In reality, if a PET scan was 50 bucks, given the
12 supply constraint of anyone competent in geriatrics
13 or AD to do a decent clinical evaluation, my guess is
14 that I, living even in Los Angeles, would probably
15 send any person that I identified a memory impairment
16 knowing the modeling that David did, directly to a
17 PET scanner. Just like we have determined, given the
18 sensitivity and specificity, I think in your own
19 work, Hal, of working up angina, that you probably
20 should send them directly to coronary angiography,
21 and do not stop, pass go, but certainly through these
22 diagnostic tests and everything.
23 The question that I come up with is, you
24 can't take these procedures in general except those
25 that are really grossly not safe or efficacious, but
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1 we haven't seen any of that, we haven't seen any
2 medicine where we're going to cure multiple sclerosis
3 by opening the back of the neck and putting a forceps
4 under the vertebral artery and tweaking it a few
5 times, and closing it up. That's not what we get
6 presented. We get presented material that's much
7 better evaluated than that but not perfectly

8 evaluated, and how does it fit into this whole
9 process of deciding what package of things are going
10 to be done.
11 And literally, the fight that exists right
12 now is between this limited budget that Medicare has,
13 how much of it is going to being spent on going back
14 to inefficient physician visits versus relatively
15 ineffective technology or effective technology, how
16 do you put all this together? And one of the things
17 that bothers me on a policy level is that with all
18 the bashing of managed care and the failure of the
19 government to stand up for managed care, we're not
20 left with anything other than going back to fee for
21 service, higher deductibles and co-insurance, and
22 fighting it out in the trenches. And we probably
23 have something to say about this as we think about
24 covering medical technology.
25 What if the neurologist had to make the
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1 case in front of us that a neurology visit for AD
2 should be covered? Could we document that anything
3 they do is value added to a good general exam, and I
4 would doubt it. And I would doubt that PET scan
5 would look better than a neurology visit, if you
6 could use cost, but I'm biased. So the question here
7 becomes how are we putting all this together.
8 And I like your point, Hal, about trying
9 to think about it in broader purposes. I don't know
10 what it would exactly look like, but I suspect that
11 even if we don't approve it, the price of PET scan
12 will come down and some private entrepreneur is going
13 to market it just like they're marketing heart scans
14 for everybody, and Medicare is going to pick up the
15 cost of evaluating the false positives and the true
16 positives, and we won't have a real coverage policy,
17 so we may spend more money on this than if we
18 actually covered it and came up with rational
19 subgroups on who it should be used. But we can't
20 bite that bullet because we can't have federal
21 guidelines or ways of using things other than sort of
22 quote, coverage decisions. So we're really up a
23 creek at the moment as far as I can tell.
24 DR. SOX: Daisy.

25 DR. ALFORD-SMITH: I guess the more I hear
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1 of this discussion, it takes me back to where we
2 started with the original mission statement, and I
3 remember quite vividly in that particular discussion
4 we had thoughts and opinions regarding the
5 comprehensiveness of what we would do, which would be
6 inclusive of various populations. And so when I see
7 Sean putting something up like the clinical impact,
8 for me I think we're beginning to speak to that. I
9 really believe that it's going to address some of
10 those things that I in particular have an interest
11 in, and I, you know, highlight the one, are there
12 specific patient selection criteria that must be
13 considered? And so it really helps us.
14 And just using one example, we're all very
15 much aware of the health disparities that exist in
16 this country and based upon that we also know that
17 there is a lack of access to a lot of the clinical
18 trials for various populations of individuals. So
19 that when you really begin to at least attempt to
20 address perhaps whether there are specific patient
21 selection criteria that needs to be considered, then
22 it also affords us the opportunity to look at a
23 broader picture of what needs to be done and
24 addressed in various subgroups of individuals.
25 So, I am particularly impressed with the
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1 additional questions, but then I also recognize the
2 limitations just in terms of how extensive do we need
3 to be, or how extensive can we really be. But if we
4 go back to that mission, it speaks to that, and these
5 questions address that particular area.
6 DR. SOX: Other comments? Barbara.
7 DR. McNEIL: Just one other comment.
8 Sean, I like your idea of grading the adequacy of the
9 evidence rather than coming out with a black or white
10 yes or no answer, I like the idea of some kind of
11 gradation, much like the professional societies do in
12 their guideline development, so I think that would be
13 a step in the right direction.
14 DR. TUNIS: I'm curious to know,
15 particularly I guess from the folks who were part of

16 the methods work group who, you know, developed the
17 interim guidelines, Alan and Hal and others, whether
18 we potentially would lose something by -- that would
19 replace a yes no question, I guess, if we did a
20 grading of evidence, and I just want to make sure
21 that sort of the thoughts around the table of what's
22 the potential risk for doing that.
23 DR. GARBER: In fact what we had said was,
24 what we lack is a direct A, B, C rating of the
25 evidence, but we rate the effect size, and I don't
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1 recall all the details of the discussion, but this
2 was an Executive Committee decision that what was
3 important was if you could draw conclusions, and the
4 reason that -- and then you would go to step two of
5 grading the size of the effect, and there were these
6 various categories that we used. As I recall,
7 though, the main reason why we didn't want to rate
8 the evidence in the first step is because we wanted
9 to give the panels discretion in deciding whether it
10 was adequate.
11 Now this decision of the executive
12 committee wasn't written in stone and it is certainly
13 something we could revisit, but the argument against
14 doing it all with the grading of evidence was we had
15 this algorithm that you go on to the second step if
16 the panel viewed the evidence as adequate in the
17 first step, and we can do the same grading, but it
18 will still be the case that you have to say what
19 threshold do you say the evidence is adequate. And I
20 think one of the advantages or disadvantages, but one
21 of the characteristics of doing it without an
22 explicit rating is it gave the panels the flexibility
23 to consider whether -- for example in some areas it
24 may be almost impossible to do a randomized
25 controlled clinical trial, and so they would have
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1 some discretion to use the lower standard of evidence
2 without making it as explicit as it would be with a
3 grading scheme.
4 Again, you know, I don't think any of us
5 felt super strongly that it had to be the way that we
6 have done it. I think it has worked pretty well the

7 way we have done it, but certainly if people think
8 it's not adequate for decision making purposes, we
9 can change it.
10 DR. SOX: Here's our customer. What do
11 you think, Sean?
12 DR. TUNIS: I think getting this feedback
13 is useful, because not of all us were part of the
14 entire history of this, and I think that in some
15 cases we found that yes-no questions on the adequacy
16 of evidence is thought to be so colinear or coequal
17 with a decision about is something reasonable and
18 necessary and therefore covered, that the MCAC saying
19 yes on that question, even when the evidence has lots
20 of significant weaknesses can in fact be something of
21 a hurdle for CMS in that it looks like the MCAC has
22 made a definitive, essentially said the equivalent of
23 yes on the coverage decision just simply based on
24 saying yes on the adequacy of evidence. And some of
25 the panels have not wanted to say no because they
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1 didn't feel like the evidence was convincingly
2 inadequate, and so you ended up in a place where you
3 had to go one place or the other. So in some of
4 those cases, as you're well aware, where the coverage
5 decision and the panel seemed to be at odds, it
6 really I think centered around this issue of the
7 difference between how good the evidence was and the
8 yes-no decision on the part of the panel.
9 DR. GARBER: Well, in the reports I am
10 familiar with, there has been a descriptive statement
11 about the quality of the evidence immediately after
12 that decision about whether the evidence is adequate,
13 and so what we're really talking about is moving it
14 out of the explanatory text into some bold faced
15 statement that it's Grade B or something, and I
16 really don't have a strong opinion about whether
17 that's important to do or not, but I would certainly,
18 I think that the panel discussions and the Executive
19 Committee discussions have been nuanced enough that
20 it would be unfortunate if the readers only looked at
21 those highlighted points.
22 DR. SOX: You know, anything that we
23 adopt, one of the reasons to do it is to improve our

24 external validity or credibility to the folks whose
25 ox may be gored by the decisions we make, or who may
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1 benefit, and do you have an opinion about whether
2 being a little more explicit about quality of
3 evidence would be helpful in that respect?
4 DR. TUNIS: I think something along the
5 lines of what Alan said, you know, of just bolding
6 and highlighting the qualitative assessment of the
7 evidence in some way so that it's clear that you
8 know, the yes-no is matched with, and here's what
9 these are, just on the scientific evidence front,
10 what the quality is, and strengths and weaknesses,
11 and I think that would be sufficient, and I think it
12 would in many cases help us to maybe formally amplify
13 it and maybe potentially formally have a vote on a
14 simple grading system.
15 So, I think we don't have to decide it
16 today, but I think this is useful input for us and we
17 may want to, with this committee's approval,
18 reconstitute the methods subgroup and try to come to
19 some consensus to bring back to the committee about
20 this stuff.
21 DR. SOX: Sounds good.
22 DR. TUNIS: Let me just do this. Jeff is
23 here, he's going to come up in a minute. Just as a
24 final bit of business, there is another panel meeting
25 scheduled for I believe it's June 12th. It's the
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1 med-surg panel and the topic is bilateral deep brain
2 stimulation for Parkinson's disease.
3 Because we are still under the old
4 operating policy and we have announced a panel
5 meeting on this topic, the executive committee will
6 be given the opportunity yet again to convene to
7 ratify that panel's recommendation. We are hoping
8 that prior to that meeting and prior to announcing
9 any future panel meetings that we will have the
10 charter revised in such a way as to no longer require
11 an executive committee ratification, and we are
12 moving along well on that front, and I will be able
13 to talk more details very soon. But their will be
14 one more executive committee meeting, probably in the

15 early fall, to talk about deep brain stimulation
16 about Parkinson's, so start reading up.
17 DR. BROOK: Is this to imply that there
18 will be no other executive committee meetings after
19 this, or do we not know, after we deal with deep
20 brain stimulation?
21 DR. TUNIS: The function of the executive
22 committee will be maintained in spirit if not in
23 fact. We are moving to being able to convene a
24 committee to deal with the broader issues of the MCAC
25 but it will probably not have the title of the
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1 executive committee, but all of your memberships are
2 intended to be maintained, and roles. It's kind of
3 in the final stages of clearance, so I just can't
4 give a lot more details about it, but your name will
5 be on a list somewhere.
6 DR. KIANG: I actually think that one good
7 way of thinking through the very discussion that you
8 had this afternoon about the role of decision
9 analysis as kind of a policy issue, I think is a
10 great thing for this kind of new committee to do and
11 advise us on, and I really think it sets the tone for
12 the panels' work. So I actually, kind of separate
13 from how we organize this, I do think that there is
14 needed desperately a role in kind of the larger
15 policy area, and someone needs to do that, and
16 somewhere we need to get kind of advice on, and I
17 would see that for whatever we call this new
18 committee.
19 But I'm sorry I missed some of the
20 discussion you had, but the very discussion you had
21 today is very important, I think, about decision
22 analysis and the role in coverage decisions, and I
23 think we need to continue to do that.
24 DR. TUNIS: That's all the business and
25 Jeff, did you want to have a few words.
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1 DR. KIANG: I wanted to actually say that
2 some of you may have heard already, but I have taken
3 a new job as the senior vice president and national
4 medical director for Sigma, up in Hartford,
5 Connecticut, it basically is their entire health

6 insurance portfolio, so I will be actually leaving
7 and my leave date is May 3rd. But I did want to say
8 that from kind of my perspective and also from the
9 Administrator's perspective, I think that we as an
10 agency have been really pleased with all of your hard
11 work and I think you have set a very important tone
12 and I don't want this issue of kind of reorganizing
13 and everything, I do see a role for this group on a
14 continued basis more in the policy making area, so
15 just bear with us as we sort through some of the
16 legal details, but the message that I wanted to send
17 is you have done a fabulous job and I really think
18 that, certainly I do, but also, I think the
19 Administrator definitely appreciates what you have
20 done here, and we are looking forward to more
21 interactions, and maybe I will have some interactions
22 in my new role at Sigma.
23 DR. SOX: Perhaps I could say speaking
24 only for myself, Jeff, that one of the reasons that
25 we have been for our success such as it has been is
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1 that we have been working for an inspired leader,
2 namely yourself.
3 DR. KIANG: Sean is inspired; I am more
4 deranged.
5 (Laughter.)
6 DR. SOX: Your boldness, your sort of
7 anti-bureaucratic approach really have been inspiring
8 to all of us, and I think it has given us confidence
9 in our government and CMS to know that people like
10 you are important decision makers in the government,
11 and speaking for myself, I'm delighted for you that
12 you're having a new opportunity, and I'm sure it's
13 the right thing to make a change for you, but we're
14 disappointed not to be able to be seeing you
15 regularly and we want you to know now highly we value
16 your help, your esteem, your inspiration. Good luck.
17 (Applause.)
18 MS. ANDERSON: There are a few closing
19 things. First of all, I do want to mention that I
20 know that most of you have to go to your respective
21 airplanes, trains, cars, whatnot, but we have been
22 invited to the conference down the hall, and that is

23 extended to our gigantic audience, I don't think they
24 would mind if you show up. You simply have to go to
25 the registration desk, they have offered us
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1 complimentary registration, they have lovely
2 exhibits, and they are having a meet and greet at
3 4:30. I think at 3:30 they're actually having a
4 discussion on who's going to pay for health care.
5 Now, for continuing information, visit our
6 web site at www.cms.hhs.gov\coverage, or simply go to
7 the CMS web site and click on the coverage process.
8 To conclude today's session, would someone
9 please move that this meeting be adjourned?
10 DR. ALFORD-SMITH: So move.
11 DR. HOLOHAN: Second.
12 MS. ANDERSON: Thanks, you all. This
13 meeting is adjourned.
14 (Whereupon, the meeting adjourned at 3:25
15 p.m.)
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