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Medicare Evidence Development & Coverage
Advisory Committee

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Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, Maryland

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PANEL PROCEEDINGS
(The meeting was called to order at 8:09 a.m., Wednesday, January 30, 2013.)
MS. ELLIS: Good morning, and welcome, committee chairperson, vice chairperson, members and guests. I am Maria Ellis, the executive secretary for the Medicare Evidence Development and Coverage Advisory Committee, MedCAC. The committee is here today to discuss beta amyloid positron emission tomography in dementia and neurodegenerative disease. The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests. Each member will be asked to disclose any financial conflicts of interest during their introduction. We ask in the interest of fairness that all persons making statements or presentations disclose if you or any member of your immediate family owns stock or has another formal financial interest in any company,
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including Internet or e-commerce organizations, that develops, manufactures, distributes and/or markets consulting, evidence reviews or analyses, or other services related to beta amyloid positron emission tomography in dementia. This includes direct financial investments, consulting fees, and significant institutional support. If you haven't already received a disclosure statement, they are available on the table outside of the room. We ask that all presenters please adhere to their time limits. We have numerous presenters to hear from today and a very tight agenda, and therefore cannot allow extra time. There is a timer at the podium that you should follow. The light will begin flashing when you have two minutes remaining and then turn red when your time is up. Please note that there is a chair for the next speaker, and please proceed to that chair when it is your turn. We ask that all speakers addressing the panel please speak directly into the mic and state your name.
For the record, voting members present

for today's meeting are Dr. Art Sedrakyan,
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Dr. Jeffrey Cozzens, Dr. Raymond Faught, Jr., Dr. A. Mark Fendrick, Dr. Steven Gutman, Dr. Paula Hartman-Stein, Dr. Susan Levine, Dr. Theresa Miskimen, Dr. Curtis Mock, Dr. Jerrold Rosenbaum, Dr. Amy Sanders and Dr. Robert Zeman. A quorum is present and no one has been recused because of conflicts of interest.
The entire panel, including nonvoting members, will participate in the voting. The voting results will be available on our website following the meeting. I ask that all panel members, please speak directly into the mic, and you may have to move the mic since we have to share.
This meeting is being webcast via CMS in addition to the transcriptionist. By your attendance you are giving consent to the use and distribution of your name, likeliness and voice during this meeting. You are also giving consent to the use and distribution of any personal identifiable information that you or others may disclose about you during today's meeting. Please do not disclose personal health information.
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If you require a taxicab, there are telephone numbers to local cab companies at the desk outside of the auditorium. Please remember to discard your trash in the trash cans located outside of this room.
And lastly, CMS guests attending today's MedCAC meeting are only permitted in the following areas of CMS single site, the main lobby, the auditorium, the lower level lobby, and the cafeteria. Any person found in any area other than those mentioned will be asked to leave the conference and will not be allowed back on CMS property again.
And now, I would like to turn the meeting over to Dr. Louis Jacques.
DR. JACQUES: Good morning. I'm Louis Jacques, I'm the director of the Coverage and Analysis Group and also the designated federal official for this meeting. I have little to say at this point other than to welcome you and thank you for coming. We look forward to a very interesting meeting.
DR. REDBERG: I am Rita Redberg, a cardiologist at UCSF Medical Center and chair for the MedCAC panel. I'm very pleased to be
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here to consider all these questions along with the help of the distinguished panel.
DR. SEDRAKYAN: Art Sedrakyan, from Weill Cornell Medical College. I'm an associate professor of cardiac surgery and public health and direct the patient-centered comparative effectiveness program, and have no conflicts of interest to disclose.
DR. REDBERG: And I have no conflicts.
DR. COZZENS: I'm Jeff Cozzens, I'm chief of neurosurgery at Southern Illinois University Medical School. I have no conflicts.
DR. FAUGHT: I'm Ed Faught, I'm a professor of neurology at Emory University, and I have no conflicts.
DR. FENDRICK: Mark Fendrick, University of Michigan. No conflicts.
DR. GUTMAN: I'm Steve Gutman, I work for a regulatory consulting firm, Myraqa, and I have no conflicts.
DR. HARTMAN-STEIN: Paula Hartman-Stein, in northeast Ohio, and I'm a clinical geropsychologist. I have no conflicts.

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DR. LEVINE: I'm Susan Levine, senior vice president of Hayes, Incorporated, which is a health technology assessment company, and I have no conflicts of interest.
DR. MISKIMEN: Theresa Miskimen, professor of psychiatry, University Behavioral Health Care, and I have no conflicts.
DR. MOCK: Curtis Mock, family medicine geriatrics, medical director, United Healthcare, I have no conflicts.
DR. ROSENBAUM: I'm Jerry Rosenbaum, chief of psychiatry at Mass General Hospital and professor of psychiatry at Harvard Medical School. I have no conflicts.
DR. SANDERS: I'm Amy Sanders, an assistant professor of neurology at the Albert Einstein College of Medicine, and I have no conflicts.
DR. ZEMAN: Hi, I'm Bob Zeman, I'm chair and professor of radiology at George Washington University, and I have no conflicts.
DR. SEAL: Brian Seal, director of health outcomes research for Bayer HealthCare. No conflicts.
DR. HERSCOVITCH: I'm Peter

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Herscovitch, director of the positron emission tomography department at the NIH Clinical

Center. I am not representing the NIH here. I have no financial conflicts.
DR. LYKETSOS: Good morning, I am Constantine Lyketsos, I'm a professor of psychiatry at Johns Hopkins, chair of psychiatry at Hopkins Bayview, and I also direct the Hopkins Memory and Alzheimer's Treatment Center. I serve as a consultant for a number of pharmaceutical companies, including Eli Lilly, who are the makers who are involved in the questions.
DR. HUTTER: Good morning, I'm Joe Hutter, medical officer in the Coverage and Analysis Group here, working with Louis Jacques, and the purpose of this meeting is to review the available evidence on the use of beta amyloid PET imaging for the management of dementia and neurodegenerative disease. CMS is most interested in the ability of this technology to inform the clinical diagnosis and management of dementia by improvement in health outcomes, particularly quality of life and patient function. We also

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seek the panel's input on whether the published evidence identifies patient characteristics that predict improved health outcomes of patients who undergo PET imaging for beta amyloid.
Alzheimer's disease is, just as a very brief background, as you know, is the number one cause of dementia in older Americans. It's fatal typically within two to 20 years and can require around-the-clock supervision and care. In 2005 it was the fifth leading cause of death in older Americans and the seventh leading cause of death overall. Currently approximately 5.4 million or roughly 12.5 percent of older Americans have Alzheimer's disease, and by 2030 that number will increase to 8.7 million. That's why the Secretary of Health and Human Services developed a national plan to address Alzheimer's disease which includes the goal, among others, of preventing and effectively treating Alzheimer's by 2025.
So we are here today to address the possible role of amyloid imaging in this workup, and while there is no definitive diagnosis other than post mortem, or any

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effective treatment to date for Alzheimer's disease, some would argue that the value of beta amyloid PET imaging is in the negative scans. If negative, it could effectively

exclude Alzheimer's disease, and therefore preclude potentially harmful and burdensome treatments in patients mistakenly diagnosed with Alzheimer's disease, it could hasten the workup for a correct diagnosis and, perhaps, for diseases that could be treated, and it could expedite and improve the quality of research to develop effective treatments for Alzheimer's disease.

The CMS authority in governing diagnostic imaging is found in the Federal Code. All diagnostic tests must be ordered by the physician who treats the beneficiary for a specific medical problem and who uses those results in the management of the beneficiary's specific medical problem.

The current coverage status is found in the National Coverage Determination Manual. Currently there is national noncoverage for all PET uses that are not specifically covered, and therefore, amyloid PET imaging is currently

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noncovered. There is no local coverage for amyloid PET imaging at this time.

MS. BURTON COACHMAN: Good morning. I am Brijet Burton Coachman, a policy analyst in the Coverage and Analysis Group, and I will be going over the voting scale and the MedCAC questions.

Starting with the voting scale, for the voting questions use the following scale identifying level of confidence, with one representing the lowest or no confidence, three representing intermediate confidence, and five representing a high level of confidence.

Voting Question Number 1.A: How confident are you that there is adequate evidence to determine whether or not PET imaging of brain beta amyloid changes health outcomes (improved, equivalent or worsened) in patients who display early symptoms or signs of cognitive dysfunction?

Voting Question Number 1.B: If there is at least intermediate confidence, which is a mean score of greater than or equal to 2.5 in Question 1.A, how confident are you that PET imaging of brain beta amyloid improves health

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outcomes in patients who demonstrate early symptoms or signs of cognitive dysfunction?

The panel discussion following Questions Number 1.A and 1.B. First we would like for you to please discuss the factors that led to your vote, and second, if there is at

least intermediate confidence that PET imaging of brain beta amyloid improves health outcomes in patients who display early symptoms or signs of cognitive dysfunction, which is a mean score of greater than or equal to 2.5 in Question 1.B, please proceed to Question 2.A. If not, please proceed to Question 3.

Voting Question 2.A: How confident are you that there is adequate evidence to identify patient characteristics that predict improved health outcomes of patients who undergo PET imaging for beta amyloid?

Discussion Question Number 2.B: If there is at least intermediate confidence that there is adequate evidence to identify patient characteristics that predict improved outcomes of patients who undergo PET imaging for beta amyloid, which is a mean score of greater than or equal to 2.5 in Question 2.A, please

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identify and discuss the relative weight of those characteristics.

Voting Question Number 3: How confident are you that these conclusions are generalizable to the Medicare beneficiary population?

Discussion Question Number 4: Please discuss any evidence gaps and the types of clinical studies that would be needed to confidently close those gaps.

Next, our five experts will discuss the current clinical workup and management of patients with cognitive impairment and possible Alzheimer's disease, the state of research, and the potential impact of beta amyloid PET imaging.

DR. REDBERG: Thanks. Next we will hear from Dr. Paul Aisen.

DR. AISEN: Thank you very much. By way of introduction, I am a physician, professor of neurosciences at the University of California San Diego. I have been treating Alzheimer's disease for over 25 years. My research interest is in the development of new treatments for Alzheimer's disease, and as such

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I have consulted extensively with the pharmaceutical industry, as you see on this slide. My research is supported by grants from NIH and private foundations, and also by contracts with industry. An additional disclosure is that I am currently discussing a new study collaboration with Eli Lilly.

So as the first speaker, I thought I

would provide a brief background on dementia and Alzheimer's disease. Dementia is not a specific illness, it's a syndrome characterized by cognitive impairment that is progressive and interferes with daily function. The most common age-related dementia is Alzheimer's disease but there's a differential diagnosis that includes vascular dementia, frontotemporal dementia and Lewy body disease primarily. The nutritional and metabolic conditions can mimic some aspects of dementia. In the United States, as you heard, it's an exploding epidemic, actually worldwide it's an exploding epidemic.

Traditionally we thought of Alzheimer's disease in this way, and I will say here that I believe that this view of the

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disease is very much changing, the field has changed dramatically over the past few years. Traditionally we thought of dementia as being a gradually progressive disorder from a mild stage where memory impairment and other cognitive dysfunction had a modest impact on daily function, gradually progressed over a period of years to severe dementia and eventually death.

For the past ten or 15 years we've considered that there was a prodromal phase called mild cognitive impairment during which there are symptoms of memory and other cognitive dysfunctions but reasonable compensation so that function remained pretty much normal.

Evaluation of an individual with cognitive symptoms or concern about dementia focuses heavily on a detailed interview. Unlike other areas of medicine, the evaluation in the dementia field involves not just the patient but the patient's family or other informants. That's usually where most of the information comes from. The establishment of the syndrome of dementia is based on this

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interview probing cognitive and behavioral symptoms and their impact on function, as well as the mental status examination.

Now there can be other aspects to the workup of dementia. Typically screens for the most common concomitant contributing factors, B-12 deficiency and hypothyroidism in older individuals is included, so blood testing for B-12 and TSH. There is more debate and less consistency about the use of formal neuropsych

testing in characterizing the cognitive impairment. Many clinicians do not rely on neuropsych testing, but rather on a brief bedside mental status examination. Structural imaging is often but not always a part of the workup, not to indicate the presence of Alzheimer's disease, but typically to look for evidence of other potentially contributing factors such as vascular disease.

Additional information can be obtained by ancillary tests including ApoE genotyping, since ApoE4 allele is by far the most important genetic contribution to sporadic Alzheimer's. A spinal tap can yield information on amyloid with A-beta levels in CSF and tau and

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phospho-tau that can be helpful in distinguishing AD from other diagnoses, and an FDG-PET can be used to help distinguish AD from frontotemporal dementia, but I will say that in most practices and certainly in my own practice, those latter three are very rarely part of the workup. The workup is heavily focused on what I have written in red, the detailed interview with the patient and family.

There are, however, diagnostic challenges, there are atypical presentations. Some individuals with Alzheimer's disease do not present with the typical predominant episodic memory impairment. There may be predominant behavioral symptoms, an early age of onset or atypical time course that decreases the confidence one has in establishing a diagnosis. If there is not good history from an informant the diagnosis can be exceedingly difficult, and there are often comorbidities in this population that also complicate diagnosis.

Now as I said at the outset, the field of AD diagnosis, treatment and research has changed dramatically over the past few years, and I would like to spend a few minutes

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introducing you to those new changes which I think are relevant to today's discussion.

Alzheimer's disease is a disease of plaques and tangles, the plaques are made up of amyloid, the tangles are intracellular occlusions of neurons. That's how Alzheimer reported it over a hundred years ago and those are still the two characteristic lesions. You cannot by definition diagnose definite Alzheimer's disease without the presence of amyloid, and that's why up until recently we have used the term probable Alzheimer's

disease, since there was no way until recently to establish that amyloid was present without brain tissue.

But in the last few years the guidelines for diagnosis have been evolving significantly, and one aspect of this are the new guidelines for pathological diagnosis of AD, which have now separated the clinical syndrome from the path diagnosis.

I won't spend much time on this because I only have a few minutes with you, but this slide summarizes what we've learned about the cell biology and the molecular mechanisms

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behind AD. In the bubble you see the pathological events that lead to those two lesions, the plaques and tangles. The plaques come from a highly amyloidogenic fragment released by proteinuric cleavage of the normal transmembrane protein APP, the amyloid precursor protein, and release of that very thick and affable fragment is thought to set in motion a sequence of events that leads to disruption of cellular function, hyper-phosphorylation of tau and formation of tangles within brain cells, and the amyloid peptide aggregates and deposits in brain tissue as amyloid plaques. So again, the pathophysiology of AD is thought to begin with the release of an amyloidogenic fragment that triggers a series of events leading to cell death.

And so to put this in simpler terms, the pivotal step in Alzheimer's disease is a cleavage of a protein with two proteolytic enzymes, beta and gamma secretase, to release an amyloidogenic fragment A-beta, which through a variety of mechanisms disrupts synaptic function and leads to neuron death.

The very compelling evidence comes

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from genetics. There's a huge amount of evidence, according to what I just said, that APP cleavage is the pivotal step in AD, but the genetics are perhaps most convincing in that every known genetic cause of AD, familial or autosomal AD, Down syndrome, they have all been closely linked to the cleavage of the amyloid precursor protein. All the genetic causes are actually mutations involving APP or gamma secretase; everything indicates that this cleavage step is the determining factor in genetic AD, and very strong evidence indicates that it's also the determining factor in sporadic AD.

And as a result, much of the drug development and research has focused on amyloid as the driving process. Trials up until recently have been conducted in the traditional diagnosed AD population which is AD dementia and most of those trials, including trials of anti-amyloid drugs, have been disappointing, they have been negative. The most encouraging data to date is what I showed you here, which is pooled data from two large pivotal trials of an anti-amyloid monoclonal antibody,

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solanezumab, that does suggest a modest slowing of cognitive decline at the dementia stage of illness. These results were just reported a few months ago.

Why, if the amyloid hypothesis is correct, has it been so hard to get clinically important benefit from anti-amyloid treatment? That comes to the new look at the formulation of AD. And here I'm showing you that the prevalence of AD is very much age-related, so it starts in the 50s but really takes off in the 70s and 80s, and age is by far the most important risk factor, and so this is showing many studies that have pointed to the association between prevalence of AD dementia and age.

But the prevalence of amyloid plaque shows the same curve but 15 years earlier, and now with the advent of PET amyloid imaging, this has been confirmed with a number of studies of amyloid PET scanning, confirming that amyloid deposits, fibrillar amyloid deposits occur in the same, with the same shape of curve, but 15 years before the onset of dementia symptoms.

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And indeed, this has contributed to our current formulation of the sequence of events in Alzheimer's disease, which is that the disease starts with fibrillar amyloid deposits in the brain and that this is followed by a series of biomarker changes that include decreased synaptic function by FDG-PET, atrophy in brain structures shown by MR, CSF changes including tau and phospho-tau accumulation marking nerve degeneration, and then eventually cognitive dysfunction and loss of function in the dementia syndrome. But we now consider that there is a continuous gradual progression from a presymptomatic, a long presymptomatic phase representing those 15 years between plaque deposition and dementia, followed by

mild cognitive impairment, and here I've indicated current descriptions of two phases of mild cognitive impairment, early and late, and the dementia syndrome which had been required for diagnosis of AD is now considered the end stage of a long process.

So we talk about the diagnosis of AD marching leftward, this is summarizing developments in the field over the last five

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years or so where we've moved away from the standard dementia stage diagnosis to the development of criteria for diagnosis of AD in the prodromal mild cognitive impairment stage, and now the acceptance of criteria for establishing diagnosis of preclinical AD, which means no symptoms, clinically normal, but with evidence by imaging or spinal fluid of amyloid accumulation in the brain. So a very changed outlook on the sequence of events and diagnosis of AD.

What gives us confidence in this formulation is evidence that even at this asymptomatic phase at which we find amyloid in brain but there are no symptoms, we see biomarker evidence that Alzheimer's disease is present and that the brain function is being disrupted. So even in the asymptomatic phase we see that the presence of amyloid is increasing atrophy as indicated in this slide by measurement of ventricular volume. So normals with amyloid have atrophy that's accelerated compared to normals without amyloid who have age-related changes.

And this translates also into

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cognitive dysfunction, so even, again, in this clinically normal phase of amyloid deposition in brain, when we study groups we can see significant cognitive impairment group-wise in those who have amyloid compared to those who don't. So the amyloid is not just sitting there, it is accelerating brain atrophy and causing cognitive change, even in this asymptomatic preclinical phase.

So this is our new paradigm now. Instead of AD requiring the presence of dementia and our use of the term probable AD meaning we have to wait until autopsy, we now have AD dementia as a definite diagnosis in someone with the syndrome of dementia and the presence of amyloid as indicated by amyloid PET or CSF examination.

Instead of mild cognitive impairment,

which is a heterogeneous term, we consider that there is prodromal AD, meaning someone who's not demented but has symptoms, and has biomarker evidence of amyloid in brain. So prodromal AD is the milder stage before dementia and preclinical AD is this asymptomatic phase of disease in which amyloid

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deposition is present, but there are no symptoms. There is a gradual continual progression from preclinical to prodromal to AD dementia.

Now, amyloid PET imaging in my opinion may be the most important recent advance in AD therapeutic research, so most of my time now is spent on drug development, and amyloid PET imaging has drastically changed the field. It has allowed us to have complete confidence in the diagnosis of AD dementia, something that was lacking before we used amyloid imaging. It has allowed a definite definition of reliable prodromal AD classification, which means mild cognitive impairment syndrome plus amyloid in brain. And it is the basis for identifying people at this most important preclinical phase, the phase at which drug development is moving. So our drug studies now are moving away from dementia, away even from prodromal AD, to focus on where we think we can do the most good, which is in preclinical AD defined by amyloid biomarkers.

Amyloid PET imaging is also highly useful in that it can reflect the

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pharmacodynamic effect of anti-amyloid treatment such as anti-amyloid monoclonal antibodies.

What about in the clinic, the clinical value of amyloid PET? Well, as you heard, a negative scan, absence of amyloid effectively rules out a diagnosis of AD, so, at any stage, at the dementia stage, at the prodromal stage, a negative scan rules out the diagnosis of AD. This can have a major impact on clinical practice of evaluation of memory disorders. A positive scan effectively assures that a diagnosis of AD is present if there are symptoms consistent with dementia.

So I'm talking now about a positive scan of a normal individual, but with the syndrome of dementia, a positive scan allows us to say definite AD, not probably AD. This is important as well, because even in expert hands, as I'll show you in a second, the

diagnosis of AD dementia has been quite inaccurate prior to the use of amyloid biomarker measurement. And a positive scan is highly prognostic in individuals with mild cognitive impairment syndrome, highly

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prognostic.
This is just showing you that from two large Phase III trials in AD dementia, in Alzheimer's disease about two-thirds of individuals have an ApoE4 allele, the most important genetic risk factor, but about a third of people with AD do not carry the E4 allele, and this slide is just showing you that in two large Phase III studies, among E4 negative individuals, one-third were misdiagnosed, as indicated by negative amyloid scanning.
So as a field, we have high confidence that amyloid PET reflects amyloid deposition in brain, and since the absence of amyloid means no AD, a third of the E4 negatives, even in well conducted studies, have been misdiagnosed.
Now, what does a positive amyloid PET scan mean in someone who is clinically normal?
I would say we've not quite reached consensus on this. The two ideas being, well, maybe it means nothing if someone has no symptoms, but I've tried to present you a framework in which I believe that a positive amyloid PET scan in someone who has no symptoms is actually

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identifying the earliest stage of Alzheimer's disease, because we can track accelerated atrophy and cognitive impairment in these individuals. We need more data on this, we need more long-term follow-up on people with positive PET scans, but I suspect that positive scan is an indication of preclinical AD in asymptomatic individuals.
I've thrown this in as a prediction, that the establishment of this formulation of preclinical AD is going to lead to the development of highly effective anti-amyloid treatment. Treatments that are only marginally effective in dementia are going to be highly effective in preclinical AD, I predict, and that will mean that eventually we will be screening the population with amyloid PET scans or spinal taps in their 50s to identify the earliest changes of amyloid dysregulation and prevent the development of AD dementia.
So to summarize what I've tried to share with you, I believe that amyloid PET

imaging is an enormously important advance, perhaps the most important advance in therapeutic research in AD. In the clinic it

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means that we no longer have to talk about probable AD dementia, we can establish the presence of amyloid and make a definite diagnosis of AD dementia and eliminate the substantial error rate in AD dementia diagnosis.

A negative scan rules out AD. As you know, Alzheimer's disease is the number one fear among aging individuals, and we can eliminate the possibility of AD at the time of scan and over the coming decade with a negative PET scan.

A positive scan plus the dementia syndrome absolutely confirms the diagnosis of AD, it's highly prognostic in MCI, and as I tried to share with you, it's an essential component of therapeutic research allowing us to move our anti-amyloid treatments into this early preclinical stage.

I would, though, caution that as I said at the outset, in most cases of AD dementia, our diagnosis is dependent primarily on skillful interview, experienced interview of a subject and informant, that is still the basis for the diagnosis of dementia and the

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most important step in the diagnosis of AD dementia, but preclinical AD is another story.

Thank you.

DR. REDBERG: Thank you, Dr. Aisen, for that comprehensive review of clinical and research on Alzheimer's dementia.

Now I would like to introduce Dr. Randall Bateman, the Charles and Joanne Knight Distinguished Professor of Surgery from Washington University School of Medicine.

DR. BATEMAN: I need to correct the introduction, it's professor of neurology, not surgery, so I don't do surgery for a living, but I do see patients with Alzheimer's disease in our clinic and general neurology patients in the hospitals, and our clinic is a memory diagnostic center so it's a specialty clinic based primarily around dementias and cognitive disorders that affect people, and these people are of wide age ranges from very young ages to much older ages that come in to see us. And I also do a significant amount of research specifically in Alzheimer's disease, and in particular with cerebrospinal fluid biomarkers

and in Alzheimer's disease caused by mutations,
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and I have been asked to present the clinical and biomarker changes in Alzheimer's disease. Here are my disclosures. Much of the research is funded by the National Institutes of Health, with additional assistance for the information I'm going to present today from private foundations, the Alzheimer's Association and other funding sources here. I'm going to describe a pharma consortium which is working to develop treatment trials for early onset autosomal dominant Alzheimer's disease, and the members are listed there, as well as the invited speaker, as a speaker that I've attended and consulting relationships that I have. I just want to highlight that Lilly is part of the DIAN pharma consortium and that we do have an ongoing study with one of their compounds that is also used in amyloid imaging, and is in that study, which is AB45 or 4B. I'd like to start by reviewing the similarities and differences between an early onset autosomal dominant Alzheimer's disease and the much more common sporadic form of Alzheimer's disease that affects people typically past the age of 65. Both start with
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the clinical presentation of memory loss and it starts subtly and is progressive in how it interferes with activities of daily living. The kind of deteriorations experienced becomes global, it affects other areas including frontal executive function and generalized cognitive decline in both diseases. The MRI, which is structural brain imaging, indicates hippocampal atrophy and whole brain atrophy in both forms of Alzheimer's disease. The amyloid imaging is largely similar for the cortical deposition of the amyloid but there's an interesting finding in the early onset cases, where there's a predominant deposition into the deeper nuclei of the brain. The glucose metabolism in both diseases is characteristic for a parieto-occipital hypometabolism which is different than other dementias such as frontotemporal dementia, and the cerebrospinal fluid findings are nearly identical, with a drop in the sizable concentration of amyloid beta 42 in the CSF, and an increase in tau or phospho-tau in the cerebrospinal fluid, which
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as Paul pointed out, are representations of the pathologic findings of Alzheimer's disease. I'm going to describe the Dominantly Inherited Alzheimer's Network, which is a funded study from the National Institute of Aging, a cooperative study of academic centers which are studying the early onset autosomal dominant form to establish an international registry of these individuals, and to study them at baseline and longitudinally after to determine the order and the rate of change of Alzheimer's disease biomarkers which can inform about the disease state. In this population the large number of mutations are from presenilin 1 and 2, which are active enzymatic components of gamma secretase, which cleave amyloid precursor proteins to make amyloid beta, and also the APP or the amyloid precursor protein, which is the protein from which amyloid beta is derived. And as Paul indicated, these are the three identified mutation genes that when mutated can lead to Alzheimer's disease in people, and have provided much of the evidence for the amyloid hypothesis.

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The population under study is largely asymptomatic with about three-quarters of individuals having no symptoms at all, while a quarter of people have already manifested symptoms of Alzheimer's disease. The age of these individuals is remarkably young, asymptomatic people are around 35 to 40, while people manifest their first symptoms of Alzheimer's disease at 45 years old. A very recent report just found a presenilin 1 mutation in the very first patient with Alzheimer's disease. August D. had brain samples from the 1906 description from Dr. Alois Alzheimer, and genetic analysis indicated that in her case she had a presenilin 1 mutation and her age of onset was also early onset, at approximately 52. The gender distribution here is as expected, with the primal age of onset being approximately 45 years old, and expected education, and ApoE for the general population. So what is the evidence for a presymptomatic Alzheimer's disease phase? I think Dr. Aisen covered this well in his presentation, and it's, from historical studies

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there was evidence that there may be a 10-to-15-year period of pathological evidence

of Alzheimer's disease preceding the clinical manifestations, and on that basis as well as biomarkers indicating changes of Alzheimer's disease in individuals, it was important to determine who will get Alzheimer's disease and when they will get it, and so this network set out to establish that with a consistent age of onset in these individuals that harbor mutations that lead to Alzheimer's disease, could we identify those who would get it based on their genetic status, and estimate when they would get their disease, and use that information. And so the sites shown here in the red participated in this observational study of mutation carriers, and the data was recently published in the New England Journal of Medicine.

And shown here is one of the figures, that at 20 years before is what we describe as the estimated years to onset, which is calculated by the parent's age at onset, subtracting the participant's age. So if the parent's onset was 45 and that person was 25,

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they would be 20 years before their estimated years to onset.

You see that the amyloid imaging by PIB PET scans shows very little if any change in the amyloid deposition between those individuals that have the causative mutations, the carriers, compared to their family members that don't have the mutation. However, by minus ten years before the estimated onset of their dementia, we already see significant deposition of amyloid throughout the cortex and in the cauda. By the time that they reach that age of expected symptom onset, which is before dementia, there is also a full load of amyloid throughout the cortex and in the cauda shown in Column C in the carriers compared to the non-carriers.

In this slide, I don't know if someone can activate the video, there is a video which will show the change over time in the amyloid deposition in the carriers compared to the non-carriers. I don't know if anyone has access to activate that, I have no control up here. Can someone just click on it?

Okay, well, I will move on. Shown in

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these graphs is the same data that was, which was meant to be shown in the video, and in these panels are different measures of Alzheimer's disease, both clinical

manifestations, cognitive measures and biomarkers. I'll first draw your attention to Panel F, amyloid beta deposition in the precuneus, an area in the cortex which changes early in Alzheimer's disease, and in this graph you can see that the non-carriers as shown in blue have a flat and stable course in their amyloid imaging where over a relative span of almost 40 years, there is no increase in these individuals in amyloid deposition at all across that entire span.

However, starting about 15 years before is significant, and it appears to start maybe a few years before that, there is an increase in the amount of amyloid deposition in the brain before these people manifest their first symptom that continues to increase approaching the time of zero, and at zero is when the first symptoms may first be noticed. And in this population they don't meet the criteria for dementia until they're 3.3 years

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past zero, it's at that stage that they meet the clinical criteria for dementia.

And so the point here is that you can see that the amyloid deposition is really fully established by the time symptoms start and by the time dementia is able to be clinically diagnosed in these individuals. Compared to that, you can see clinical measures of cognitive impairment such as in Panel B, the mini-mental status examination, showing significant changes in the group up to five years before the estimated age of onset, reaching criteria for dementia, as I stated, three years after, in a clinical dementia rating box, so this CDR scale is a sensitive clinical measure of functional and cognitive impairment which is administered by a clinician evaluating both the patient and an informant which tells about their symptoms, and similarly you can see changes there, significant changes there about five years before symptom onset.

In addition to this, other changes occur such as brain atrophy, decreased glucose metabolism which has been well described before, increase in the cerebrospinal fluid

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tau, the protein component of the tangles in Alzheimer's disease, and a decrease in cerebrospinal fluid amyloid beta 42, the main component of the amyloid plaques, while in the plasma the level is elevated in these individuals due to their mutations.

And so this information together represents a data set which predicts a cascade of events which lead to cognitive impairment and dementia in autosomal dominant Alzheimer's disease. This is summarized in this graph showing the relative differences between these biomarker measures, amyloid beta deposition shown in orange, and the clinical measures, the clinical dementia rating from the boxes, shown in black, to compare the chronology.

And so, what is the relationship between other biomarkers which we use clinically today? Today in the clinic if there's a question about the diagnosis of Alzheimer's disease there are specialized tests that we can use, and those include the glucose metabolism PET scan as well as cerebrospinal fluid biomarkers, to aid in the diagnosis of a questionable case of dementia or the cause of

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dementia, and typically in early onset cases we use these tests to help better define both what is the diagnosis as well as alternative causes of cognitive impairment which would be treated in different ways. And it's also used in later onset cases when there is a question as to what's causing the patient's cognitive impairment.

And so shown in these graphs is the relationship between cerebrospinal fluid amyloid beta 42 concentration and amyloid deposition as measured by PIB PET scans. And you can see that in this population of late onset Alzheimer's disease, there's a very tight correlation between those individuals that have low amyloid beta 42 representing high amyloid deposition in the brain, so that on the X axis as we have increasing amyloid deposition, all of those individuals have low cerebrospinal fluid amyloid beta 42, and so we use that CSF measure to predict this.

Conversely, you see that above 500 picograms per mil on the CST test, that all of those individuals or nearly all of those individuals have no amyloid deposition.

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However, up to around 20 percent of those individuals will have low CSF amyloid beta 42, which would predict they have high amyloid; however, the amyloid scan doesn't show that, and so that discordance creates some question concerned with if those individuals, if their dementia is due to Alzheimer's disease, and it's clear that the amyloid imaging has an

added value in interpreting some of these results.
So the interim conclusions of the ongoing DIAN longitudinal study are that a large number of people have been enrolled, and that there's a pathological cascade of events which leads us to the first cognitive symptoms of sporadic AD dementia, and that may start as early as 15 to 20 years before their symptom onset, and that the first clinical and cognitive changes that can be measured in a research study start at five years prior to the estimated age of onset, but in the individual patient these tests are not as sensitive, and the autosomal dominant Alzheimer's disease population represents an informative group of individuals to study for sporadic Alzheimer's

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disease.
So, I want to highlight a few points about the population and then talk a bit more about clinical trials and approaches for treating these, and how these are being used for developing treatments for Alzheimer's disease, including in the prevention mode.
So, I think Paul explained well that current therapeutic trials may be too late.
One point to highlight is that it's nearly universal that people with these mutations will develop Alzheimer's disease, and they were able to predict when they would develop it, and that many of the treatments have been, proposed treatments have been developed on these mutations.
And so DIAN is starting some treatment trials in cooperation with partners from the Alzheimer's Association and in multiple pharmaceutical companies as part of the DIAN pharma consortium to test multiple different drugs in this population in parallel to determine which are likely to have beneficial results. And I just want to highlight that we're using these biomarker measures, including

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amyloid imaging in the brain, to make decisions about drugs and their likelihood of benefit in this population, so that the biomarker outcomes of this Phase II study in autosomal dominant Alzheimer's disease will be used to make decisions about which drugs will be expanded and continued for Phase III studies to demonstrate a clinical and cognitive benefit.
So the relationship of the amyloid imaging to Alzheimer's disease is strong enough that as a

group of scientists and physicians, we believe that we can make informed decisions about how to do therapeutic trials. And shown here are some of the candidate drugs as well as the biomarker outcome, that primary measure that will be used, and you can see that cerebrospinal fluid amyloid beta and PIB PET measures are central when we proceed in this process. This is a summary of the trial design which I will pass through for the sake of time, and the trial design is meant to have a continual process of evaluating drugs moving forward and using these in prevention trials. So, how powerful are these measures?

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You can see here a power analysis based on the number of individuals needed, that with only 32 people in each group, we can have very very highly powered studies to detect these effects, that the predicted effects of the drug with these measures are precise enough in the research setting that we can get very useful information from a relatively smaller number of people in the research entity, and this speaks to the specificity of these measures and the clinical trials. I would like to just review a historical precedent of what may be some of the earlier biomarkers in the cardiovascular field. And so, many of us are familiar with the story of how statins or HMG-CoA reductase inhibitors were developed to treat and prevent atherosclerosis, but there's a very interesting case history here where one of the first statins was actually used in a population of people who had mutations that caused familial hypercholesterolemia, and the biomarker I'm referring to is cholesterol deposition in the soft tissues of the body. And so shown on the left pretreatment

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is the xanthomas from cholesterol deposition in the tissue in a young woman with familial hypercholesterolemia, which resolved in the panel on the right with just a few months of treatment with a statin drug, and this was one of the first clinical signs that those drugs could be useful in the prevention of heart attacks and stroke. And so I'll finish with this slide, proposing that we may be able to use PET amyloid imaging scanning for the same purpose. Thank you.

DR. REDBERG: Thank you very much, Dr. Bateman, for that summary of the research in clinical areas, and now I'm going to introduce Dr. Steve Pearson, from the Institute for Clinical and Economic Review, and MGH's Institute for Technology Assessment.

DR. PEARSON: Good morning, everybody. So first, disclosures. The Institute for Clinical and Economic Review is an academic research group, we're not an independent organization. We are based at the Massachusetts General Hospital, as Dr. Redberg said. I want it to be clear that the basis for

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my comments today are borne out of a white paper that our research group did with the strong input of a policy development group. The title of the white paper was Diagnostic Tests for Alzheimer's Disease: Generating and Evaluating Evidence to Inform Insurance Coverage Policy. The funding for the paper came from unrestricted funding that was given to our hospital for ICER activities generally from many sources: Aetna, Harvard Pilgrim Health Plan, Health Partners, Merck, the National Pharmaceutical Council and the United Health Foundation. I personally have no financial or other conflicts of interest on this topic.

So, the genesis of this white paper actually was Gina Kolata's articles in the New York Times. Many of you may remember, she started writing articles about how new diagnostic tests were becoming available, there was a lot of interest among patients and families regarding them, and this struck many of us in the health technology assessment world as kind of, in some ways similar to old stories in which people are so focused on generating

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evidence for the therapeutic agents in a disease area that the evidence behind diagnostic approaches kind of comes in as a stepchild and doesn't get as much attention, and then all of a sudden there's this concern that we have a treatable condition and we don't know as much about the diagnostic approach as we really should know, especially if we're going to be considering anything like population-wide screening.

So we decided to pull together an Alzheimer's disease diagnostic policy development group with representatives from really all the stakeholders we wanted

perspectives from. We wanted it to be a dialogue because we wanted researchers and manufacturers and patients and insurers to sit together and to wrestle with what would good evidence look like for an Alzheimer's diagnostic test, where are we today, where will we be, or where will we need to be as we start to develop more therapeutically effective agents.

So the representatives, and there's a list available, I'm sure, in the document

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itself, of clinical researchers in the United States; patient organizations, the Alzheimer's organization in specific; private and public health insurers, including representatives from Aetna, Blue Cross Blue Shield of Massachusetts, Kaiser, WellPoint; and we did have one staff member from the Coverage and Analysis Group at CMS; and manufacturers, Avid Radiopharmaceuticals and Johnson & Johnson.

Now as you can imagine with this kind of group, pure consensus was never the goal, learning and dialogue was, so the opinions that were reflected in the white paper are actually strongly representative of the comments and opinions of the group as a whole, but it should in no way be taken as representative of the specific opinions or perspectives of any individual person on that group. So what I'm going to say today is mainly a distillation of what that group had to say reflected through my own personal lens.

All right. We've already heard the MedCAC question. The words again, which are familiar to those of you who have been to MedCAC, are the issue of changing health

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outcome. That is, you know, whether imaging changes health outcomes, improved, equivalent or worse.

So, in the white paper we also go through an overview of how the paradigm of Alzheimer's disease has been evolving and what the role of biomarkers is in that picture.

Now, it's really important to recognize, and you've heard from the earlier presentations today, the biomarkers have many different possible functions in the research and potentially the clinical arena. There is just no doubt that biomarkers are useful in identifying patients who have amyloid in their brain, and if you're developing a drug that tries to reduce amyloid in the brain, it would

be very nice to recruit patients who have amyloid in the brain. So this is kind of self-evident, and groups like European Medicines Agency has formally qualified PET imaging as a tool for enriching the patient populations of therapeutic trials so that you get patients who have the pathology that you're trying to treat.

So there are research uses, and we'll

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turn to the clinical uses. It's important to point out, though, that the correspondence between AD pathology and symptoms, they're not always consistent. It's easy to forget that given that the scans obviously can show you what you think you're looking at, amyloid in the brain, but 30 percent of cognitively normal older adults have positive amyloid findings in the brain. Again, those in the HDA world will remember how often a routine MRI of the spine will show a herniated disc in patients who do not have symptoms. So there have always been questions about the correspondence between findings on scans and the clinical evolution.

So the current dominant view is what you've heard, that there is an amyloid deposition that develops first, and then there's a 10-to-15 or even longer year phase, preclinical phase, with symptoms appearing later and accelerating.

Now, this new paradigm is at the foundation of the new criteria for diagnosis that were put forth from a 2011 workgroup that was convened by the National Institute on Aging and the Alzheimer's Association. I want to try

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to be brief here, but they still -- and again, there are disagreements about this in their research and clinical communities, there are still different terms being used for the different phases of Alzheimer's disease. So in this paper, the work out of this workgroup, preclinical Alzheimer's disease is a disease for research purposes only, that's their words, and they divide that into three different categories, asymptomatic amyloidosis, amyloidosis plus neurodegeneration, and amyloidosis plus neurodegeneration plus subtle cognitive decline, that's preclinical Alzheimer's disease in this framework.

Then mild cognitive impairment, which is diagnosed with core clinical criteria, that's the interview and often some kind of mental status test, questionnaire or survey

that's given to make that diagnosis. And again, in this framework, amyloid and neuronal injury tests such as PET imaging are framed as affecting the likelihood that MCI is due to AD. And this gets more specific in the category of true AD dementia, where again, the diagnosis is made by the core clinical criteria and the

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biomarker tests are used only to lend a relative likelihood of that AD dementia due to AD. So again, the words probable, possible and likely, and there are ways that different kinds of biomarker tests fit together to give you these different likelihoods.

So coming out of this group's work, one of their important quotes, I think, was that there was a broad consensus within all three workgroups that were divided into preclinical, mild and AD dementia, across these groups there was broad consensus that much additional work is needed to validate the application of biomarkers for diagnostic purposes. All right.

So, one of the things that our white paper tried to do was, again, share perspectives on how evidence is looked at by technology assessment groups and, by extension, payers, when they look at a body of evidence. And so we walked through with this group different ways of looking at a body of evidence. I'm going to present briefly an analytic framework approach thinking about evidence on diagnostic tests for Alzheimer's,

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an evidence hierarchy approach and linked to that a set of terms, analytic validity, clinical validity and clinical utility.

So this is a very busy analytic framework but it's vastly simplified. What this tries to show is the chain of events that would occur in the evaluation of a patient with memory complaints or at risk of Alzheimer's disease. Again, it could be someone that doesn't have their own complaints but family members are concerned, or has some other predisposition. The clinical evaluation happens first.

I'm not going to walk through all of these but the point is that right now without further diagnostic testing, if the clinical evaluation is positive, the patient could go for targeted treatment for Alzheimer's disease. If the clinical decision is negative, the decision could be not to do any treatment, no

AD targeted treatment. A negative could also lead to further diagnostic testing for other conditions.
Out of all of these boxes, you can just see all of these, again, negative and

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positive arrows coming out. The main point to make is that with an analytic framework you grasp that you can't judge the effect on patient outcomes through harms and benefits simply by looking at diagnostic accuracy, a test versus some standard. It has to be viewed as how this test would be used in a flow of clinical decision-making, and in a flow of patient reactions and outcomes. So it's not a simple, as simple as looking to see how accurate a test is in measuring what it says it's measuring.
So I tried to come up, this is not in the white paper, but I tried to come up because I was asked specifically for PET imaging, to try to come up with a list of potential benefits and harms that would be something you might want to consider measuring in tests, diagnostic tests, not just PET amyloid but all.
So briefly, the potential benefits of a positive test could be the ability to start AD-specific treatment earlier, the ability to plan more effectively for the future of the patient and their family, the ability to seek out clinical trials. But we have to recognize

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that there are potential harms of either positive or false positive tests. The harms could be additional patients who are being started on drugs with limited or no benefit, there could be discrimination or difficulty obtaining long-term care or life insurance based on diagnostic approaches.
And then the potential benefit for the negative test, which in this case I think are going to be spoken of a lot, are that it promotes consideration of alternative and perhaps more treatable causes, it can reassure patients and families, and it may reduce the number of patients who are either continued or started on drugs. However, there are also potential harms with negative or false negative tests, especially false negative tests if there's aggressive additional diagnostic testing that does not lead to improved outcome and may present unnecessary risks and costs, or false patient reassurance from a false negative.

Now I'm not saying what the chances of each of these are, but this is just a kind of bucket list of I think important potential

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harms and benefits of diagnostic testing, including PET amyloid.

So how do we start to, again, think about these potential harms and benefits? Well, a very frequently used hierarchy of evidence for diagnostics is this one on the left here, it's the Fryback and Thornbury approach that was originally created for radiology evidence but it can be linked loosely with genetic testing evidence categories such as analytic validity, clinical validity and clinical utility, and so I put them together here.

So as you can see at the very top of this, you've got the issue of technical efficacy, and that's basically evidence on whether the scans can be read, whether there's reliability of testing, whether you do the same test twice on the same patient and get the same result, these kinds of technical effects.

Diagnostic accuracy is where we often spend a lot of time discussing diagnostic tests because that involves issues around sensitivity and specificity versus some gold standard. Beyond that, though, is where you start to get closer

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to patient outcomes at the fifth level.

So between diagnostic accuracy and patient outcomes, there are tests that can study diagnostic impression. These are tests that study whether there is a change in a presumptive diagnosis after a doctor receives a test result. Beyond that, you can study whether doctors or patients actually take different actions, so not just that they say they feel differently or have more confidence in the diagnosis, do they actually change their practice, do they change drug treatments, do they change further diagnostic testing, et cetera. And then obviously, you could study the impact of all of these changes, potential changes on patient outcomes. And lastly, the vital outcomes which would include cost effectiveness. So I want to drill down a little bit more into the potential harms and benefits, looking at a review of the current evidence first.

So, our literature review in its search terms was really looking more for diagnostic accuracy, so we are undercounting

here the number of studies that have been done
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on technical efficacy, and I will discuss some of the findings but this is not a complete history of the world of technical efficacy, certainly of all the diagnostic tests available for, potential tests for Alzheimer's. But just from this, again from this spread here, you can see that the vast majority of studies available look at the diagnostic accuracy, a small handful have looked at diagnostic impression. None to date have, that I'm aware of still today, have actually measured whether doctors do change their behavior. None have looked at patient outcomes or societal outcomes.
So if we separate out the studies just on PET amyloid imaging, again, I just left the technical efficacy box blank, but there were 14 from our original set that looked at clinical validity or diagnostic accuracy and one that looked at diagnostic impression.
So let's walk through some of the data. These are data that come from the FDA label, from the review of the FDA, and these data were published in an article by Clark, et al. in 2012, although the data are actually presented somewhat differently in that article,
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some of the numbers are framed differently. So this was a study that the FDA had actually asked the company to go back and expand from a first set of data that was presented in 2011. When they came back they had 59 patients who had been enrolled, they'd enrolled a lot of patients who were within the last six months of life, and these patients consented to have PET scans, and then if they died there was an autopsy that allowed for a correlation to be made between what the scan showed and what the autopsy showed.
And looking at sensitivity and specificity, you can see the way the test was done, there were five trained radiologists -- actually I'm not even sure if they were radiologists or nuclear medicine specialists, but there were five specialists who were trained to read these and they read them independently, and the sensitivity of those who received in-person training from another specialist in how to read these was, the median was 92, that means obviously half were above that and half were below it, the range among the five readers in sensitivity was 69 percent
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to 95 percent. With a different kind of training of how to read these scans the sensitive was lower, it was 82 percent, with a range from 69 to 92 percent. As for specificity, again, the median among those trained in person was 95 percent, the range 90 to 100, and the same for those trained through electronic media training.

Also available in the FDA information is just a raw count of the false positives and false negatives, so out of the 59 scans that each reader was asked to read, each reader had one or two false positives. And the false negatives, there were somewhat different ranges, although there's a typo here. For those who received in-person training the range was between two to 12 false negatives per 59 scans, and for electronic training, three to 12 false negatives per reader over 59 scans. So that's, I think the core, the best evidence that I'm aware of, certainly the best single study on the diagnostic accuracy, if you will, of PET amyloid imaging.

But there are other things, again, other ways the test could be used, and I've got

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to go quickly here, so I'm going to go through just a couple other studies.

People have talked about whether you can get useful prognostic clinical validity from PET amyloid, so in one industry-funded and co-authored study by Doraiswamy, again last year, they took 151 subjects who had PET amyloid imaging and were followed longitudinally, and of these, 69 started out cognitively normal, 51 had mild clinical impairment, and 31 had clinically diagnosed AD dementia.

What they found is that the A-beta positive scans were associated with greater decline in multiple cognitive outcome measures, and I think their chief finding was that the conversion, if you have a patient who's just got mild symptoms and you want to tell them what's your risk of progressing to more serious dementia in the near term, what they found is that over 18 months of follow-up, 29 percent of those with positive scans converted to full dementia and 10 percent of those with negative scans converted to full dementia. So even those with negative scans are progressing but there is a greater likelihood of progression or

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a higher likelihood among those with a positive scan.

I'm probably, I'm seeing the blinking light, so I'm going to skip through my questions, and if the panel would like to come back to them later, there's some issues about each of these important studies that are probably worth discussing.

So briefly, again to try to wrap up, again, there is one study as you may remember from that table, in which there has been a published work looking at its effect on diagnostic impression, what action did it spawn, or nonaction. This was also an industry-sponsored and co-authored article. They had 229 patients who had been selected by memory disorder specialists themselves who were asked to basically pick patients for whom they thought the results of amyloid imaging would be helpful. They gave a working diagnosis and a management plan before they wrote down the answer to the question, what would you do with this patient right now if you were going to start to care for them? And then they received the PET image results and they were asked

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afterwards, what would you do now, what is your current diagnostic impression and what would you do now? So they were able to evaluate the difference in what they said they would do before and what they said they would do after.

Now the diagnosis changed in 55 percent of cases, but it's important to recognize that the diagnoses were given originally in three categories, probable AD dementia, indeterminate, or probably not due to AD, and so a lot of the switching happened from the indeterminate pile going into either probable, you know, likely AD or not AD.

They also found that 87 percent had changes to the diagnostic or management plan. I shouldn't say had, the doctors expressed that they would likely have changed the diagnostic or management plan. There again, that's a mix of different things, it could be a change in the drug that a patient was on, it could be a change in whether the patient would be referred to a clinical trial, a fair number of these changes in clinical management were whether the patient would or would not be referred to a clinical trial, and there were suggested

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changes in further diagnostic management.

So just a few of these, I think, are very important, because this is the closest on that hierarchy scale, the closest that we get

formally to patient outcomes, looking at diagnostic impressions. So again, what you'll see is you've got patients who the clinicians believe their symptoms are not due to AD or are indeterminate, they're changing to due to AD on the basis of the scan. Now that could be viewed as very clinically useful, but I think on reflection it's important also to remember that 30 percent of cognitively normal adults have beta amyloid in their brain and so a question is, is finding it in a patient with dementia a 100 percent guarantee that that patient has Alzheimer's dementia and nothing else.

Potentially useful, definitely. Ten or about 12 percent of the 86 patients who were thought to have AD had negative scans, and you can imagine as a clinician that that would be a patient for whom you would likely think very differently afterwards if you thought it was probable AD and then you get a completely

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negative scan.

There were some interesting aspects of what the doctors said they would change in their management. So again, is adding AD drugs to amyloid-positive patients the right thing to do, does that produce positive net benefit for these patients? Among those patients who had negative scans, doctors reduced their current, among those who were currently on medication, it dropped from 50 percent to 25 percent, so doctors kept a fair number of patients on their Alzheimer's drugs even after they, said they would keep them on their Alzheimer's drugs even after a negative scan.

There was reported intent to reduce other diagnostic testing for patients with positive scans, and there was a similar drop in other testing for patients with negative scans that to me was not easily explained. If you have a negative scan, the rates of intended CT, MRI, other investigations dropped, so maybe one of the clinicians in the field can explain why either positive or negative results would lead to doctors saying they would do further testing.

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I'm going to ask for guidance from the panel because the light's blinking. Do you want me to wrap up? Okay.

What I'm sure we will come back to is in the white paper there's a reflection on what insurers will be looking for, and a set of

specific research design recommendations. And these both look at the current time, if you will, when the available treatments for Alzheimer's disease are acknowledged by most to have limited effectiveness, and it's looking forward to the trials that are being designed right now and are being launched that are going to be looking for new therapeutic agents to work and how we can build in things like nested marker by treatment interaction studies to improve the data that we can get on diagnostic studies when we do, which we all hope find a more therapeutically effective agent. Thank you.

DR. REDBERG: Thanks very much, Steve, for that overview and going through all the literature.

Next I would like to introduce Dr. William Thies, who is the chief medical and

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scientific officer from the Alzheimer's Association, and if you didn't already, could you just mention any conflicts of interest for funding purposes for the association?

DR. THIES: Well, my name is Bill Thies, I'm a full-time employee of the Alzheimer's Association, and you can judge your conflicts from that. The association receives about 98 percent of its income from individual donors. We have a small corporate income that, most comes from the sponsorship of the Alzheimer's Association International Conference. Lilly has been a sponsor in the past and we hope will continue to be.

So I'm going to talk to you about two things, so I'm sure this talk is not going to be quite as eloquent as the previous presenters. And the first is our experience with the development of an appropriate use document for amyloid imaging, and the intent of that document was to give medical professionals the best advice we could at this point in time on the value of amyloid imaging and dealing with people with complaints of cognitive difficulties, and let me get to the right

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button. I needed an orientation before I started.

So the appropriate use document that we did in cooperation with the Society for Nuclear Medicine and Molecular Imaging, the people on the task force that developed the document are all household names if you live in an amyloid imaging household. They're

essentially leaders in the field, with a few of us from the organizations included. And I'm going to change the order a little bit here. The intent of this document really was to offer what advice we could at this point in time. It was essentially using modern methodology for these kinds of documents. Conflicts of interest, we paid close attention to, these are the rules. I'm going to not read these slides to you because I know we can all read. The process really was pretty much the order of all consensus documents through an evidence assessment, and the questions being developed. I think the only thing that maybe was a little different is that this document was opened for public comment to virtually all of the Alzheimer's community, and they had

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several weeks where they could make comments, and those comments were taken into consideration, adjustments in the paper were made, and there was a revoting period on the indications.

Evidence review is pretty much standard methodology. You can see the magnitude of what was found in terms of the number of publications screened and those that were actually used, and the group rated indications and non-indications. In some ways while this was titled an appropriate use document, it may be as well regarded as an inappropriate use document.

One of the things that I think is important to recognize is the paper itself goes into some detail that we should not look at amyloid imaging in isolation but it fits within a context of evaluation of the patient, and that includes the very important evaluation by a dementia expert and referral to a PET scan if it's appropriate. And one of the things that it spends some time on is it's really talking about the disclosure of the information in the PET image. One of the things that's perfectly

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clear is that in many of the research studies, people who have been imaged are blinded to that result where in a clinical setting that's not going to be the case, and it's really important that that disclosure is done in a way that makes it perfectly clear what the information from that PET scan really offers to the patient.

So, appropriate uses. People with cognitive complaints, a possible diagnosis of

Alzheimer's disease and the knowledge of presence or the absence of amyloid pathology could change the diagnostic confidence. So what kind of patients actually look like this? The appropriate uses that were indicated included patients with persistent progressive unexplained mild cognitive impairment. These are people who don't reach the criteria of dementia but are in the predementia standpoint. And one of the things that I think has become perfectly clear if you look at current literature is the malignancy of a diagnosis of mild cognitive impairment with a positive biomarker signature for Alzheimer's disease is quite significant, most of those people

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consistently and rapidly move on to dementia, and a diagnosis of MCI with a negative biomarker signal for Alzheimer's disease is considerably less malignant and some of the modern studies show that only a few percent of those people go on to dementia. So I think this is a very significant piece of information.

The other group of patients that I think can be affected are patients with an unclear clinical presentation, so these are patients that don't present with classical memory-based cognitive dysfunction, don't fit into the typical age group for people with Alzheimer's disease, all of the various things that might make you question whether it's a diagnosis of Alzheimer's disease or something else, and I would ask you to just keep that in mind as we get to the second part of the presentation, which is really talking about some of the experience with patients.

And finally, people with progressive dementia with an early age of onset, which is a group that typically has less Alzheimer's disease and more other dementing illnesses, and

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in the same way that the 30-year-old woman dies in an emergency room from myocardial infarction, they're frequently misdiagnosed because somebody in their 40s doesn't have Alzheimer's disease, so I think this is a very important group to pay attention to.

Now, the consensus group also identified a number of inappropriate uses specifically, so people that have typical Alzheimer's disease do not need an amyloid scan, it's perfectly clear, people who are clearly defined as having Alzheimer's disease

and in clear stages of dementia are not going to get any benefit from it, and I think this eliminates a large portion of the population that might be considered for scanning. As it stands right now, the link between amyloid accumulation and dementia severity is quite limited, and so this is not a tool for actually suggesting it might help stage people with dementia, it really is not useful for that, not appropriate to use. There's no reason to scan everybody who is ApoE4. We already know that people with ApoE4 are likely to have more amyloid accumulation,

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and there's not much additional information generated for these patients. Patients with cognitive complaints that are unconfirmed with clinical examinations, this is a little bit of a difficult group, but the fact is that if you cannot identify with the sort of standard tests that we have now the difficulty with cognitive function, there's probably not much value to doing amyloid imaging. It does not substitute genotyping for suspected autosomal mutation carriers, and so this is supplementary information and it shouldn't replace that kind of genetic analysis in appropriate families. Asymptomatic screening, the association has a fairly long history of being relatively negative on screening asymptomatic people for Alzheimer's disease, and certainly this comes out no different in the discussion of the group. And finally, nonmedical usage, I think this is particularly important as this technique becomes available in the general community. It's not useful for the assessment

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of competency or judging activities of daily living, particularly elements like driving, which can be controversial. So what's the impact of the installation of these appropriate use criteria? We suspect greater physician confidence, the reduction in other tests as you've seen from some of the data, and a decrease in the use of sequential neuropsychological testing, which is often quite difficult for patients and really expensive to the system. I might just make a comment around greater physician confidence. One of the things that I think is important to recognize

is that it's not just the confidence of one individual physician, but it's confidence within the whole system in the documentation of the diagnosis. It is clear that if the only advantage you're going to get from the information that comes from this test is in the modification of people's treatment of their Alzheimer's disease with a pharmacological entity and a measurable medical outcome, there are strong limitations to that value. The fact is that anyone who has looked

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at the CMS data knows that one of the drivers of cost for patients is if they're cognitively intact or not. So if you take two sets of patients that have similar comorbidities, one is demented, one is not, what you see is the demented population has roughly three times the cost inside the system. That's only money. What it really reflects is the fact that the individual with dementia and the other comorbidities has an increased level of utilization of medical care, often because they cannot be incorporated into patient care for chronic disease in a way that a patient who is cognitively intact is. And so the confidence and the documentation of diagnosis of Alzheimer's disease in the system has a very high likelihood of improving the level of medical care for other diseases, and I think we need to keep that in mind.

So let's talk a little bit about the second part of this discussion, which is really an effort that we made to try to collect patient experiences and patient outlooks on possible testing of this sort. We have a group that we identified as our early stage advisors;

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they're a group of patients with early stage Alzheimer's disease that come in and help the association really understand their needs and understand how we can best service those people, and they're a wonderful resource for the association, their volunteering for us is really a major benefit.

And so in a series of interviews with those people, there were a number of things that came out fairly clearly and consistent. One is certainly the confidence in the diagnosis affects the access to appropriate treatments, but in addition to that there's a variety of nonmedical, nonpharmacological services that people with Alzheimer's disease need, and they can do a much better job of

really building the care team, finding the support services that they need. Also, if they're identified early, they have a much greater chance of being included in a clinical trial, which not only gives them the potential to be exposed to beneficial medication, but certainly moves the field forward. Planning is a major issue for people with Alzheimer's disease, the sooner they're

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diagnosed, the earlier they can begin planning and the better they're going to function. It's also clear from a large body of scientific information that families that understand that one of their members has Alzheimer's disease and understands it as a disease cope better with the disease, and so an early diagnosis certainly helps in that regard. So, some of this is a little bit redundant, and I'm happy to express that as my own inadequacy in putting together presentations, but I want to share some of the blame with CMS, because their rules said we had to put slides in by December 15th. And I have to tell you, as I was hearing all the earlier presentations, I knew how to make mine a whole lot better but I couldn't sit down there and change my Power Point presentation before this was done. So, apologies for the redundancy, but one of the things I want you to understand is that in this early stage group it was quite clear that many of them had a very prolonged period where their diagnosis was in question, as long as nine years, and they had typical

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characteristics that included the fact that they either presented at an early age or a very early stage, or an atypical presentation. Often they appeared while they were still working if they appeared at an early stage, and they were having workplace problems. But the bank executive who was having trouble doing routine arithmetic is a classic example of someone who is not appearing with a classically memory-based cognitive difficulty and those people are not well diagnosed, they're given all sorts of options about burning out, middle age crisis, all sorts of vague diagnoses that have no medical entity, and frankly, they're tortured for many years until they finally get a diagnosis of Alzheimer's disease. So a test that helps us really identify those people who are going to go on to

Alzheimer's dementia now eases their anxiety, it eliminates a long expensive period of diagnostic procedures, it can in fact result in a profound benefit to the individual depending on whether they have long-term disability insurance or not, and maybe most importantly for the person, there is a decrease in anxiety

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with a confident diagnosis, and there is the ability to come to closure around a diagnosis and move on with the rest of their life and get on with all the important planning issues that they're going to have to attack.

So, in the setting of what we've already talked about, the recommendation of the Alzheimer's Association is that essentially the findings of the appropriate use group are accepted for reimbursement by CMS and that the inappropriate uses are not, and you can read the slide.

And I have just one other point, and that is in association with SNMMI. We recognize that continuing physician education is going to be required in order to maximize the value of this new diagnostic technique.

Thank you for your attention.

DR. REDBERG: Thank you, Dr. Thies, for representing the views of the Alzheimer's Association.

And the last of our speakers right now is, before the break is Dr. Mark Mintun, the chief medical officer of Avid Radiopharmaceuticals, a wholly owned subsidiary

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of Eli Lilly.

DR. MINTUN: Good morning. I would like to thank CMS and MedCAC for your invitation to speak on behalf of Eli Lilly and Avid Radiopharmaceuticals. In addition to telling you that I'm the chief medical officer at Avid Radiopharmaceuticals, I thought it would be important to introduce myself a bit further. Before joining Avid Radiopharmaceuticals in 2010 I spent my entire career in academic medicine, mostly at the Washington University in St. Louis. I'm a nuclear medicine physician, board certified in 1985, and have spent countless hours in radiology reading rooms looking at everything from brain scans to bone scans to lung scans, but in 1980 I started getting involved in brain imaging research, and I have continued that, and until I left for Avid Radiopharmaceuticals, I had been continuously funded by the NIH for

radioimaging research for over a quarter of a century. But perhaps more pertinent is that in 2003 I started a program at Washington University in coordination with the Alzheimer's

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Disease Research Center for amyloid imaging. By the time I left in 2010, my group and I had done over a thousand carbon-11 PIB brain amyloid imaging scans, and in fact that data contributes heavily to what you've seen so far by the different groups this morning. But during that time I realized that we need to translate imaging research like this into better patient care, so I left for Avid Radiopharmaceuticals to join a team that was working very hard to convert our growing knowledge of brain amyloid imaging into a technology that could benefit patients. So what I'm going to talk to you about today in the next 20 minutes is to present the existing data as a logical chain, how this beta amyloid imaging connects to improved outcomes for Medicare beneficiaries. The first part of that is going to be reviewing that diagnosing Alzheimer's disease is a challenge for physicians, you've already heard some of that, and this represents a significant clinical unmet need. Also, we're going to talk about Amyvid as an FDA-approved beta amyloid imaging agent

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that is reliable and accurate, an intrinsic utility in assisting physicians to make a more accurate diagnosis, and we'll talk a little more about that. But then the more accurate diagnosis leads to more appropriate management and selection of appropriate treatments, both of which we believe predict improved outcomes. But to put this in context, one of the things we have to keep in mind is that the unmet need in Alzheimer's disease is so large and so significant, it led Congress and the HHS to establish a national priority shown here by the National Alzheimer's Project Act. A key part of this priority mentioned several times in the Act is that improved care is needed, but improved care starts with an early and correct diagnosis. I think Bill mentioned that multiple times. But despite this prioritization as outlined in NAPA, we also learned this morning from Dr. Hutter's slide that there's actually a preemptive non-coverage policy on beta amyloid

imaging, and this had occurred prior to any review of the evidence you're hearing today. So we do have an important job today. We're

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going to discuss the evidence, does it support the revision of this preemptive decision, and our hope is that we're going to give you the information you need on the panel to conclude with confidence that amyloid imaging can help Medicare beneficiaries, and we believe put us one more step further to respond to this call for action.

So let's review the challenges of diagnosing Alzheimer's disease. Well, you've already heard that Alzheimer's disease is a clinical pathological disease entity. This means that the clinical findings are actually not sufficient to definitively diagnose Alzheimer's disease, but require additional neuropathological findings, typically obtained at death.

So furthermore, the presence of amyloid is a required component of this neuropathological finding, so what that means is without amyloid plaques in the brain, the patient does not have Alzheimer's disease. So what happens when clinicians don't have the benefit of autopsy data?

This slide summarizes eight different

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studies over a period of 15 years that indicates the level of false positives at autopsy in patients that were clinically diagnosed during life with Alzheimer's disease. As you can see, the rate of false positives hovers around 20 percent, and this basically means that one out of five patients is probably, one out of five patients who are diagnosed with Alzheimer's disease, probably do not have that disease. So there's misdiagnosis, there's incorrect diagnosis. Does that matter? Do we care? And I would argue that yes, we do care.

So I've highlighted here just a few of the types of reasons that we should care. As you notice on the top row, we talk about treatments. Now earlier we mentioned the fact that it's frustrating not having great treatments for Alzheimer's disease. Do we have no treatment? Actually we do have four FDA-approved treatments that are reimbursed by Medicare, and these treatments are indicated for symptomatic treatment of Alzheimer's disease. Their effects are modest. However,

they are not known to have efficacy in
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frontotemporal disease, which is another diagnosis that can be confused with Alzheimer's disease but it does not have amyloid, and in fact can exacerbate behavioral symptoms.
On the second row, we have to remember that misdiagnosing somebody with Alzheimer's disease means that a physician can miss an opportunity to treat the actual cause of their cognitive decline. Some of those problems can be reversible, and I highlight depression and hydrocephalus as potential causes that might not get adequate treatment if a patient is misdiagnosed.
But finally on the last row, something we heard about from Bill a little earlier, an uncertain or missed diagnosis can prevent families and patients from making informed decisions in how to deal with the daily challenges of a family member with a dementing illness and appropriately planning for the future.
So let's specifically talk about the data for Amyvid. Just to clear up a milestone, set of milestones here, the first paper on the ability to image amyloid in the brain was done
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in 2004. There has been involvement with the FDA with not one but two FDA advisory committees starting in 2008, and then recently, as of April of this year, the FDA approved the first amyloid imaging agent, Amyvid.
Now one thing I can add since this slide was done, as Bill pointed out, back in December, is that the European Union agency, the EMA has also recently approved Amyvid for use in Europe.
So let's actually review the data that led to those approvals. There's actually quite a few Phase I and Phase II studies that look at the technical aspects of the scan, and I'm going to focus really on the clinical Phase III pivotal trials. So what was the first study?
The first study was a, looked at Amyvid scans and compared them with histopathology. The results demonstrated a correlation between the scan and the histopathology to a correlation of .78 and the P value was highly significant, about .0001, so this study demonstrated the technical efficacy of use of Amyvid to image amyloid.
There was a second study. This study
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focused on the diagnostic performance of Amyvid. So in this study readers were asked to interpret Amyvid scans in a binary, in other words positive or negative for beta amyloid plaques, and again, their results were compared to pathology. Using this majority interpretation across two types of data sets, there was a 92 to 96 percent sensitivity and 100 percent specificity for being able to predict the pathology. So this study demonstrated the diagnostic performance of the Amyvid scan.

For the third study, now we shift a little bit. Now we go from the tracer, the scan, to the reader. In the third study the primary goal was how reliably images could be read; in other words, if you take the same scan and put it in front of different imaging physicians, would they read it the same way? So these readers were trained with electronic media-based training. This was something that allowed themselves to train themselves essentially, no intervention by somebody else, in their own office at their own pace. And then after they finished the training, they

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went on to read scans from 151 subjects. The overall results are shown by this kappa score. Basically the scans were read reliably and reproducibly and indeed, another way to look at this is that the agreement between the readers was over 90 percent. Now of course one of the things we also want to do is summarize the performance of those individual readers in the last two studies in terms of diagnostic performance so this is, and I wish I had a pointer here, let's see if that's what that is.

So if you look at the patients who went to autopsy within one year of imaging, in other words, the ones where the autopsy and scans were close together in time and give the best representation of validation of each other, the median sensitivity and median specificity of the typical reader were in the range of 90 percent or greater for both in-person training and electronic media training.

So to recap, study one demonstrated the technical performance of imaging amyloid as a tracer, study two demonstrated the diagnostic

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performance for predicting pathology, study three demonstrated the ability for the scans to

be read in a reliable fashion.
Now by the way, since both in-person training and electronic media training were successful after the drug had been approved, Eli Lilly is continuing to offer both types of training depending on what the imaging physician would like, how they would like to be trained and how they think of themselves and their particular needs. And so in-person training and electronic media is going to continue, and electronic media training is available at all times on the web.
I want to also point out for completeness that adverse reactions were reported, and I can certainly answer any questions having to do with the safety.
So the data I just showed you led to an FDA approval with the following indication, and I urge you to read the entire indication but I'm just going to call out the first sentence. Amyvid is indicated for PET imaging of the brain to estimate beta amyloid neuritic plaque density in adult patients with cognitive

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impairment being evaluated for Alzheimer's disease and other causes of cognitive decline.
And I note that in the context of your Question 2, this identifies the specific population with clinical utility.
Now it goes on and gives you a way to use Amyvid. A negative Amyvid scan indicates sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of Alzheimer's disease at the time of image acquisition. So the implication is that has clinical utility. Where did the FDA, how did the FDA reach this conclusion of clinical utility?
That's a very important question that you have to consider, but one of the things that we have is that the FDA reviewers actually authored a paper that appeared in the New England Journal of Medicine September 6, 2012, that speaks directly to this deliberative decision they made, and I quote: Two FDA advisory committees, this is in the paper, endorsed the implicit clinical value of information obtained from brain beta amyloid imaging. The regulatory approval was based on

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this endorsement and on clinical data showing sufficient scan reliability and performance characteristics.
Okay. So now let's move on a little

bit to the way it would be used. I think it's really timely that the appropriate use criteria just was published a few days ago. I don't have to go over this, I'm not going to be redundant, but I do want to point out that all of the areas of appropriate use that they've identified actually fall within the label that we just heard. In a way these appropriate use criteria are a way of operationalizing the indications of clinical utility that was determined by the FDA and, as I point out, this gives you further confidence when you address Question 2 in identifying what is the population that would benefit.

So we've discussed our FDA registration trial on technical efficacy and diagnostic accuracy, you've seen this sort of hierarchical theme. The FDA determined that the clinical utility is implicit given the information provided by this test. The combination of technical efficacy, diagnostic

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accuracy and this implicit clinical utility, we believe should be enough to give one confidence that beta amyloid imaging will improve outcomes in Medicare beneficiaries.

That said, as you know, we've gone on and done additional research. We have studies looking at diagnostic thinking and therapeutic efficacy, and so I'm going to turn to those now to sort of flesh this picture out a little further.

So, I'm going to spend a minute on this slide. A13 was really our first attempt to look at the impact of Amyvid on diagnostic thinking. Academic neurologists reviewed case vignettes from scans and patients enrolled in our Phase II trial. And it is of note that in cases in which the diagnosis changed was about 56 percent, but there was specific limitations to this study. Nevertheless, it was actually very reassuring that in 2012, Schipke published a study that actually reinforces the findings of our A13 study on diagnostic thinking and intended change in management, but with a completely different tracer, this was florbetaben, not florbetapir. This is a

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different tracer. And in this study there was an impact on diagnostic confidence as well as in intended patient management in almost 90 percent of the cases.

But again, these studies have significant limitations and what I'd like to do

is focus on A17. You've heard a little bit about this earlier, I think we need to go through it a little more carefully now.

So our study A17, reported by Grundman in 2012, we have 229 patients that were enrolled with a history of cognitive decline and an uncertain diagnosis that included Alzheimer's disease. Some of them had already completed a workup, others were in the midst of a workup for their cognitive decline, but all of them had been carefully evaluated by a physician. That physician had a diagnosis and a diagnostic confidence in their current treatment and testing plan, if relevant, recorded. That physician then was able to get an Amyvid scan as part of this trial and the results were returned to them, about roughly half of them were positive and half of them were negative, and then they had to repeat

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their assessment of the diagnosis, diagnostic confidence, and their current plan for management in view of this Amyvid scan. So what happened?

Well, there's a lot of results on this page and the next one and the next one, but I just want to highlight a couple things. 55 percent of the cases that physicians reported they changed their diagnosis, and in almost all the patients the physician had an increase in diagnostic confidence in the post-scan diagnosis, an average of 20 percent.

But as I think, to address some of the tables that Steve talked about this morning, let's dig into this a little better. There were actually 86 patients that had a diagnosis of Alzheimer's disease, and that's certain, they didn't necessarily meet these core criteria that we heard about, there was a degree of uncertainty but that was the diagnosis. Of those 86, 33 actually had a negative scan, the negative scan category. 33 had a negative scan. That's roughly 40 percent of the patients in this study who actually had a negative scan, and in that the doctors

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changed their diagnosis 97 percent of the time.

So this is an example of how the effect of a scan can change diagnosis.

Now, we talked about the diagnosis being changed. In treatment, one area that the people whose workup was in progress did indeed, a positive scan led to a 30 percent decrease in use of brain structural imaging by CT and MRI,

and a 47 percent decrease in neuropsychological testing. The negative scan also had some decreases in use of testing, probably due to the increased confidence the physicians had after both negative and positive scans in their diagnostic workup.

Also note at the bottom that of the, across all study subjects, there was a change in the plan of at least one intended treatment, in at least one change in their management, in 87 percent. Now I don't have it on this slide, but I think relevant to some of the things that Bill brought up just a minute ago, many of these changes in addition to this and some medication changes that I'll talk about, were actually specifically related to this value of knowing. In other words, in 22

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percent of the cases, physicians reported that they would change their recommendation for how to counsel the patient and family on driving and other home safety issues. 16 percent of the time the physicians changed their recommendation on how to enroll in clinical trial, Steve mentioned that. But also, 20 percent of the time they changed their recommendation on counseling the patient and obtaining support services.

So, what about intended medication? We've heard about this, we know there's limitations in the ability of these medications to alter this disease. But I point out that these AD medications shown here, these are the four FDA-approved medications demonstrated to have efficacy, in the amyloid-negative subjects there was a big drop, not 100 percent, and that would be I think appropriate given people's knowledge, but a very large drop in the use of medications in these groups. In the subset which had amyloid-positive scans, there was an increase, almost 30 percent, in the use of medications. Now I also note in the amyloid-negative subjects there is a hint that people

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were looking for other potential treatments as there was an increase in psychiatric medications such as antidepressants in that group.

So to summarize, we identified the unmet clinical need that stems from the difficulty in diagnosing Alzheimer's disease, and the result is that patients commonly, perhaps one in five or more, carry the wrong diagnosis of Alzheimer's disease even to their

deaths. We established that the safety, efficacy and reliability of Amyvid as an FDA-approved drug for imaging beta amyloid, there is implicit clinical utility for ruling out Alzheimer's disease with a negative scan. And we also learned that the FDA identified patient characteristics which are within the approved label and, furthermore, these have been operationalized by the appropriate use criteria. And actually, continued data has been collected and there's ongoing collecting in this area of amyloid imaging to the point that there is now evidence that supports that amyloid scans will change management, including management of drugs that are indicated for

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Alzheimer's disease.

So I guess what I'm saying is that you should not consider any one study, if we consider the totality of the evidence, the scientific studies, many of which you've heard this morning, the implicit clinical utility established by the FDA, established by committees convened by the FDA, the consensus panel of clinical experts for appropriate use that we heard about from Bill -- and then also, I want to point out the recommendation by the largest Alzheimer's patient advocacy group in the United States. Given this totality of data, I believe you can confidently conclude that amyloid imaging results in an improvement in diagnosis, more appropriate management, and therefore, should give improved outcomes for that clearly defined Medicare beneficiary population. Thank you very much.

DR. REDBERG: Thank you, Mintun, and we will now take a ten-minute break. We will be back at 10:24.

(Recess.)

DR. REDBERG: Dr. Salloway. Thanks very much. I will introduce Dr. Stephen

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Salloway, director of neurology and the Memory and Aging Program at Butler Hospital, and professor of neurology and psychiatry at the Brown University Medical School.

DR. SALLOWAY: Good morning. You stole my first line. Those are the slides for the next presenter, I have no slides to present.

I'm a cognitive neurologist specializing in dementia care and research for over 20 years. During that time I've seen thousands of patients with Alzheimer's disease

and related disorders. Our program has tested all of the amyloid PET tracers currently in development, and my hospital has received research support for this work. I have no major conflicts with any of these entities. I came here today at my own expense and my views represent those of a dementia expert advocating for better tools to improve care for our patients and families.

As you've heard this morning, the foundation of good medical care rests on an accurate diagnosis. Patients and families want to know what is causing the loss of memory,

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language and thinking abilities. Amyloid PET is a major advance in the diagnosis and treatment of Alzheimer's disease. Previously we had to wait for a postmortem examination to definitively diagnose AD. Now with amyloid tests we're able to safely and reliably detect fibrillar forms of amyloid, one of the hallmarks of the disease.

Let me describe two patients that demonstrate the benefits this test offers to patients and families. The first is a 67-year-old woman with mild memory loss and depression. She was becoming repetitive and misplacing items. She was also upset and tearful about the breakup from her fiance. She was working full time cleaning in an office and driving. Her mother and older brother had dementia. Her brain MRI was normal. She had MCI level of cognitive impairment but it was unclear whether the cognitive impairment was due to depression or an early stage of AD. An amyloid PET scan was clearly positive. After the test I told her with a high level of confidence that she has MCI due to Alzheimer's disease, MCI patients with a

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positive amyloid scan progress to dementia at a high rate, and we spent the next two visits discussing disease management. Her sister agreed to help monitor her bill paying, driving and work responsibilities. Her sister also decided to move in with her for companionship and day-to-day assistance. The patient decided to start treatment with donepezil and to enroll in a clinical trial with an anti-amyloid agent to try to slow decline in memory. A negative amyloid scan would have had a very different care and outcome.

The second patient, 66-year-old retired principal, had difficulty with talking

but preserved short-term memory. The differential diagnosis included limbic-sparing Alzheimer's or progressive aphasia due to frontotemporal dementia. A brain MRI showed nonspecific atrophy, and FDG-PET showed an AD pattern. An amyloid PET scan was clearly negative. I made a confident diagnosis of progressive nonfluent aphasia due to frontotemporal dementia. The cholinesterase inhibitor was stopped and an anti-amyloid trial was not recommended. The family was educated

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to expect a significant decline in speaking, writing and spelling, and to monitor carefully for behavioral symptoms. He may be eligible for new trials of medications for frontotemporal dementia.

In both cases the amyloid scan contributed to a clear diagnosis and a more definitive treatment plan. As you heard this morning, the FDA required that amyloid PET scans strongly correlate with postmortem examination, and they met that standard.

Hundreds of terminally ill patients made a selfless contribution in their final days to help make this advance in the fight against Alzheimer's.

Should I tell my patients that we have a test available to help clarify their diagnosis but we can't use it because Medicare doesn't cover it? Instead, we have to wait a few years to see how symptoms develop. That's the approach from the last century when these tools were not available. America leads the world in the latest advances and highest standard of medical care. Let's continue that high standard, especially for our vulnerable

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elderly, our parents and grandparents, and honor the dedication of the hundreds of terminally ill patients who made this breakthrough a reality.

I strongly support the appropriate use guidelines proposed by the SNMMI working group as an excellent approach to guide clinical practice and reimbursement. They recommend that amyloid PET be considered by a dementia expert after a thorough evaluation in cases of progressive unexplained MCI, cognitive decline in patients under 65, and cases with diagnostic uncertainty in which AD is a likely possibility. These are excellent recommendations to carry forward into clinical practice and both of my patients fit these

criteria.
Let's build on the precedent established by this committee with the approval of FDG-PET --
DR. REDBERG: Your time is up.
DR. SALLOWAY: Five seconds -- and make an accurate diagnosis and the best treatment available to the cleaning woman and the principal, as well as the corporate
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executive who can afford to pay for the test. Thank you.
DR. REDBERG: Thank you very much, Dr. Salloway. I'm going to introduce Dr. Fillit, executive director and chief scientific officer of the Alzheimer's Drug Discovery Foundation. I'll give everyone a 30-second warning, as we do have a lot of speakers and we really need to stay on time so we can get to everybody.
DR. FILLIT: Thank you for inviting me here today. Like the other speakers, I have been taking care of people with Alzheimer's disease for over 35 years. I am the executive director of the Alzheimer's Drug Discovery Foundation. Our foundation had the privilege of providing seed funding for the program at the University of Pennsylvania from 2002 to 2004 and, as a result, our foundation receives a pro rata share of royalty payments to the University of Pennsylvania, but I receive no personal compensation, and I'm only speaking here as a practicing geriatrician in New York City. I have done some consulting with Eli Lilly, which is unrelated to the use of Amyvid
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in clinical practice.
I want to present four cases from my practice that help illustrate the use of Amyvid and its value. The first patient was an 80-year-old man that I saw, came to me complaining of memory problems, his wife complained of them. He was a highly proficient executive who had built a number of companies, traveled all over the world. The complaint was that the memory problems were interfering with his daily life and his work. He had a stressful life with many risk factors, he went to a lot of business dinners and drank alcohol, he traveled a lot and got jet lag a lot so he was taking sleeping pills. He didn't exercise. My psychometric evaluation revealed significant impairment in immediate and delayed recall. An MRI and other tests were normal.

I thought that he had amnestic MCI from Alzheimer's disease but I nevertheless recommended lifestyle changes, including moderation of his business activity and travel, you know, stopping the sleeping pills, and reducing his alcohol, and exercising, and I started him on Alzheimer's therapy.

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When I saw him again three months later he was much better, but I told the family that -- they said how can he be better if he has Alzheimer's, and I said well, 50 percent of people with MCI might get better with lifestyle interventions and 50 percent might not, but that even if he had Alzheimer's, he still might have Alzheimer's disease, but by reducing these risk factors I could help him to become better, but he still might have Alzheimer's, and there was the risk that he would continue to progress. And so this was a very high functioning man, serving on a lot of board of directors, and wanted to work, his whole life was work. The family really had placed a great value on knowing and it was very important to his wife, so we did the Amyvid scan, and somewhat to my surprise, I must admit, it was negative.

And this really changed his life, because now he could confidently remain in the business that he devoted his life to, he could remain on boards, he didn't have to resign from life, he could remain actively involved. I took him off his Alzheimer meds, he continued

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his lifestyle interventions, and the family was very grateful for being able to get the Amyvid scan, and it illustrates the value of how a negative scan can provide reassurance, prevent a false positive clinical diagnosis of Alzheimer's disease that would result in loss of independence, and avoid unnecessary treatment with anti-dementia therapies.

My second case is a 75-year-old man with an unusual history of progressive dementia over a period of 12 years. He came to me for consultation because no one could quite tell him what was wrong. He had had a prior history of multiple falls from a horse with head trauma. At initial consultation ten years ago the MRI showed hydrocephalus, but his clinical presentation did not show urinary incontinence or gait disorder so the surgeons declined to give him a shunt, and he was given a presumptive diagnosis of Alzheimer's disease.

My evaluation indicated the presence of mild dementia but the cause was unclear. The family sought a definitive diagnosis and placed a great value on knowing for the purposes of prognosis and care planning.

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An Amyvid scan was negative. This supported the real likelihood that the patient's dementia was due to hydrocephalus and suggested the possibility that if the Amyvid scan had been available ten years ago, he might have had a shunt and a better clinical outcome, and it certainly illustrates the potential value of the scan in accurate clinical diagnosis, differential diagnosis, and treatment for that matter.

The third case is a 75-year-old man --

DR. REDBERG: 30 seconds remaining.

DR. FILLIT: -- with a typical course of Alzheimer's disease who I first saw in the MCI stages, and basically the Amyvid scan encouraged him to enter clinical trial.

And for my last, then, it is a 59-year-old woman, early onset of cognitive impairment, episodes of confusion, who couldn't get a diagnosis. I thought she had Alzheimer's disease possibly due to MCI stage, and basically in ten seconds what I will say is that this woman could not afford a scan, and today she was forced to resign from work. She does not have a definitive diagnosis, she

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cannot get disability, and her life is in limbo while she waits for a definitive diagnosis from the test of time.

DR. REDBERG: Thank you, Dr. Fillit.

Our next speaker is Dr. Norman Foster, director of the Center for Alzheimer's Care, Imaging and Research, chief of the division of cognitive neurology and professor at the Brain Institute, University of Utah.

DR. FOSTER: Thank you. I'm a board certified geriatric neurologist who personally cares for patients with cognitive disorders. I'm also a member of the committee that developed appropriate use criteria. I do not benefit financially by the performance of imaging studies. I'm here to represent and advocate on behalf of my patients. I have paid my own travel and lodging expenses, and have not received any honorarium or payment for my attendance or comments today. Throughout my career I have done research in molecular imaging and I consider myself expert in using

imaging for clinical decision-making. My conflicts of interest are listed here. Amyloid PET can remove much of the

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certainty and disagreement about the cause of cognitive problems that currently inhibits clinical decision-making and contributes to inconsistent poor quality care. We're currently not doing a very good job in providing dementia care, and amyloid PET imaging would help. As with all diseases, a confident, timely, accurate diagnosis is the key to appropriate management. As with all diseases, knowing the underlying disease pathology aids diagnosis, in this case whether or not amyloid is present in the brain. Let's be clear about treatment. It is not just prescribing medications. Default treatment for patients now is all too often a sedated, restrained, institutionalized patient without a specific diagnosis. With amyloid PET it will no longer be possible for providers to explain that they can't diagnose Alzheimer's disease. I share with others the apprehension that nonexpert use of amyloid PET imaging would lead to frequent misdiagnoses. However, this can be addressed by reimbursement that reflects appropriate use guidelines. Indiscriminate use would be financially unfeasible. However,

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concern about overuse of this technology is overblown. As described in more detail in my written statement, I found in our specialty dementia clinic, amyloid imaging would be very helpful in about 20 percent, somewhat helpful in 20 percent, and unnecessary or inappropriate in 60 percent. Thus in Utah, amyloid imaging would be appropriate for two to three percent of people with dementia and MCI following appropriate use criteria. While I think that more patients than this might benefit, this is the current situation where diagnosis and treatment of dementing diseases is such a low medical priority. Three of my Medicare patients currently are awaiting amyloid PET imaging and illustrate how this test could improve outcomes. The first case is a 76-year-old Ivy League law school graduate who developed paranoid schizophrenia in his 40s. He was no longer employable but was able to live independently in a small town until three years ago, when he became unable to manage his daily

affairs. He was admitted to a psychiatric
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hospital, given a diagnosis of Alzheimer's disease and discharged to a nursing home. I saw the patient at the request of the family, who felt that his diagnosis had been inadequate. In fact we performed the first MRI brain scan and found that he had evidence of unreported remote head trauma. When I saw him he was delusional and psychotic, but also had significant cognitive disturbance, cognitive deficits. Is this really Alzheimer's disease or is this a person who's psychotic with worsening triggered by his head injury? If his amyloid PET scan is positive, he has Alzheimer's disease and should be continued on medications for Alzheimer's dementia --
DR. REDBERG: 30 seconds remaining.
DR. FOSTER: -- but he wouldn't qualify for state psychiatric services. If his amyloid PET scan is negative, then the symptoms are due to psychiatric illness and he requires more intensive treatment, but unfortunately, he would no longer be able to be cared for in this nursing home.
Additional cases that I have presented show that other areas are equally important in
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the complex kinds of patients that we deal with. Thank you.
DR. REDBERG: Thank you, Dr. Foster. Next up, I will introduce my former medical school classmate, Dr. Sam Gandy, professor of neurology and psychiatry at Mount Sinai, and chair in Alzheimer's research.
DR. GANDY: Thank you, Dr. Redberg. I have spent the last 26 years as an NIH-funded researcher developing amyloid-lowering drugs, primarily as a basic scientist, but I also am a cell biologist and neurologist, and I'm coming here primarily in my role as a member of the faculty practice at Mount Sinai. We were early adopters of florbetapir scanning soon after the approval this spring, and so I'm going to just show you sort of a real world consecutive series as much as Mount Sinai reflects the real world, which is a tertiary urban referral center, and these were actually collected together with Effie Mitsis, another professor at Mount Sinai.
I have no financial associations with Lilly or Abbott. I have served on the DSMB of Pfizer, Janssen in a vaccination trial, and I
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have basic science grant funding for the laboratory from Baxter and from Amicus Therapeutics.

In our center the impact on diagnosis really refers to whether patients are referred for clinical trials, and out of the first 20 consecutive patients that we studied, I think it's safe to say that the ones in whom the Amyvid scan was most telling were those with unusual presentations, and that represented nine out of the first 20, and since the numbers of 20 don't really mean anything, I didn't represent them as fractions, but here are the five types of unusual patients we saw in this first 20. The most common are, in whom the diagnosis was confusing or had been confusing are patients with either a language or a behavioral presentation, and what seems to be the case in our experience is that that presentation over age 70 is usually Alzheimer's disease, and around age 50 or below is usually FTD, but we've established that in this series.

Rapidly progressive dementia: we had one 50-year-old man who basically from April to November went from supervising 75 bank

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employees to not knowing his age or the date.

In this particular subject there was an important role in therapy because he had a hypercoagulable state and was thought to be harboring an occult cancer, and the diagnosis he was ostensibly carrying before the florbetapir scanning was of limbic encephalitis.

In two other cases depression sort of dominated the picture, and when the MCI had been static for several years.

So, just the individuals are summarized on the next two slides. You can see those with PPA who had negative scans were in their 60s and the positive scans were in their 70s or above and had Alzheimer's disease, and were referred. A combination of Parkinson's and Alzheimer's was sorted out best with Amyvid scanning, but in these two subjects it could not have been distinguished whether they had Parkinson's with dementia or both Parkinson's and Alzheimer's without the Amyvid scan.

The last group of subjects, in those who had AD, they typically had mild dementia and wanted a secure diagnosis and preferred a

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scan over a lumbar puncture.

DR. REDBERG: 30 seconds.

DR. GANDY: Finally, two unusual subjects. A former football player who was repeatedly concussed at every game. We saw him, five neuropsychologists at Mount Sinai saw him and split three to two on the diagnosis, Amyvid resolved it, and he did not have Alzheimer's disease.

The last one was a 59-year-old man with a history of traumatic brain injury, and turned out to have frontotemporal dementia and focal lambertosis.

DR. REDBERG: Thank you, Dr. Gandy. Our next speaker is Dr. Carl Sadowsky, medical director of the Premier Research Institute and clinical professor of neurology at Nova University.

DR. SADOWSKY: I'm Dr. Sadowsky, I'm a clinical neurologist and very active in clinical trials, and I'm here representing the real world. These are my disclosures. And I would like to sort of add some faces to the statistics and present in a very abbreviated fashion three cases, and the first

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question that is addressed by the panel, is there adequate evidence that PET amyloid imaging changes health outcomes in patients with early symptoms and signs of cognitive dysfunction, and I will illustrate that it does.

The first case is a 72-year-old primary care physician with a several-year history of memory loss that is worse in the last six months. He was concerned he was developing Alzheimer's disease, that he was considering retiring from his practice. He saw one of his colleagues and he was started on donepezil. He came for evaluation and MCI was diagnosed. He was referred for an amyloid scan, which was negative. It was determined that his risk for his current mild cognitive diagnosis was very low. This was based on data from about a three-year multicenter longitudinal trial suggesting that amyloid-negative mild cognitive impairment or cognitively normal subjects are unlikely to experience significant cognitive deterioration with progress to dementia in the three years following evaluation. The reference is on the

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slide.

He was dramatically reassured, we stopped the donepezil, and he returned happily to his practice.

Case two was a 69-year-old management executive brought to the office by his wife after she realized he did not remember several conversations. He still handled finances for his corporation but not quite as quickly as before, and made some uncharacteristic mistakes. After careful workup, the diagnosis was mild cognitive impairment. He had heard about and requested amyloid imaging. His scan was positive. Subjects, and again the reference is on the slide, with mild cognitive impairment with higher levels of cortical amyloid on PET scan are at higher risk for future cognitive progression than individuals with lower levels of amyloid on their scan. This risk factor was explained to him, he has entered into a clinical trial with an amyloid-lowering agent. He is being a little more careful at work, particularly with financial documents. He has reviewed his own personal financial plans and is making certain

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they reflect his current and future wishes. The last case is an 83-year-old man with a history of memory loss of three or four years. Recently some unsteadiness developed. He had mild urinary incontinence after prostate cancer treatment. An MRI scan was ordered, demonstrated some moderate hydrocephalus with mild cortical atrophy and some widening of the Sylvian fissure. Evaluation yielded moderate dementia and the issue of hydrocephalus was raised. As part of his workup an amyloid PET scan was ordered and was positive. After discussion with the family it was decided not to proceed with an LP to evaluate the patient for possible ventricular shunt. The positive scan made us believe that a significant component of the dementia was related to plaque pathology and the main cause of his dementia was probably due to Alzheimer's disease. The risk-benefit analysis of considering a shunt with his history and positive amyloid scan seemed poor. Patient was started on donepezil and subsequently memantine was ordered. These types of cases have led me to

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some practical guidelines for amyloid imaging, and I just think it's interesting that I came up with my thoughts without hearing any of the other reports. I think imaging should be considered in mild cognitive impairment to stratify amyloid-positive and amyloid-negative

scans, in atypical cases including early onset and for differentiating from frontotemporal dementia. I think we would be much less likely to image if there's no impairment or it's a screening procedure.
DR. REDBERG: 30 seconds remaining.
DR. SADOWSKY: And in long-term patients with classical history of Alzheimer's disease with typical decline, amyloid scans are unlikely to significantly alter treatment.
Thank you.
DR. REDBERG: Thank you, Dr. Sadowsky. Next is Dr. Mykol Larvie, who is with the department of radiology and nuclear medicine at Mass General Hospital and director of neuroimaging there. He is representing the American Society of Neuroradiology and the American Society of Functional Neuroradiology.
DR. LARVIE: Thank you. I would like

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to -- well, first, my name is Mykol Larvie, and I am representing the American Society of Neuroradiology and the American Society for Functional Neuroradiology. Together these are professional societies, they include approximately 5,000 physicians, and in our clinical role we attempt to the best of our ability to be objective patient advocates, and that's the point of view I would like to represent here.
I would like to acknowledge the efforts of the committee and the participants in this exercise, and I would like to emphasize that amyloid imaging has been a triumph of basic science investigation, translational research beginning with the work of Chet Mathis and Bill Klunk, and now we have a clinical product. So I think this is a tremendous opportunity to advance neuroscience and I want to acknowledge that and thank all the participants.
So, I derive no financial benefits from any related enterprise. I have participated in clinical trials but have not received personal or research support. I also

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will skip some slides that are redundant with other speakers.
So, in the evaluation of neurocognitive deficits imaging plays a significant role and we can do many things. We look for irreversible disease that may affect management such as stroke, brain injury. We look for treatable conditions that might

improve patient outcomes like hydrocephalus, hemorrhage and the like, and then we seek specific diagnosis of neurodegenerative diseases. Our evaluation, or the imaging is done in the context of overall evaluation of the patient that includes clinical examination and laboratory studies, and I would like to emphasize that there are multiple imaging modalities available to us, including CT, MRI, and both FDG and now amyloid PET. So in some cases, such as shown here, this is the first published account by Bill Klunk and colleagues, showing the striking distinction between a normal brain and an Alzheimer's disease-affected brain in comparison to relatively mild changes seen on FDG-PET, so in some cases amyloid imaging makes

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a profound, it makes diagnosis profoundly accurate and confident. So, we realize there are many benefits in diagnosis, including, I'd like to point out, as has been emphasized by other speakers, the ability to make appropriate life planning choices. So in other cases where we have, we acknowledge that there is a spectrum of amyloidosis, you see on the top row an amyloid scan of a patient with mild Alzheimer's disease and you can see a relatively large burden of amyloid within the brain in a distribution typical for Alzheimer's disease, in contrast to an 82-year-old clinically healthy man with no significant abnormal amyloid uptake, so in some cases diagnosis is easy and accurate. We acknowledge that there are risks of inaccurate diagnosis, both in terms of false negative and false positive, and one would acknowledge the stigma that attends a diagnosis of Alzheimer's. We need to acknowledge this, that it may jeopardize people's standing in the community, their employment and their health insurance, and we want to be very careful to use this appropriately.

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So, there is this problem of asymptomatic amyloidosis, it may represent a preclinical Alzheimer's disease state, or these patients may not progress to Alzheimer's disease. Shown here are a number of different brain scans showing different degrees of amyloidosis. On the far end of the spectrum it's fairly easy, amyloid-negative and normal cognition, it would be a normal diagnosis. On the other end we have amyloid-positive with a

clinical diagnosis of Alzheimer's disease which makes it very easy. In the middle we have different degrees of amyloidosis that may correlate variably with the clinical syndrome, these are the problem cases in which we need all possible diagnostic modalities.

So, I'm going to skip these. We acknowledge that there has been demonstrated utility in both improving the accuracy of diagnosis and guiding management in Alzheimer's disease, and we acknowledge --

DR. REDBERG: 30 seconds remaining.

DR. LARVIE: -- there's a range of coverage options.

So we make some specific

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recommendations. Firstly, we believe that amyloid PET imaging is in the best interest of patient care and should be covered by CMS. We believe that improved patient outcomes are a primary objective and that we should be careful to guide our practice to appropriate patient outcomes. Amyloid PET imaging interpretations should be standardized and high quality so that it is not the cause of increased inaccurate diagnoses.

We, I should note we concur with the SNMMI guidelines for appropriate utilization, and in particular we note that we should not be doing amyloid screening outside of IRB-approved research studies now.

DR. REDBERG: Thank you, Dr. Larvie.

DR. LARVIE: Thank you.

DR. REDBERG: The next speaker with be Dr. Richard Wahl, director of the division of nuclear medicine and PET scanning at the Johns Hopkins Hospital, and he is representing the World Molecular Imaging Society.

DR. WAHL: Good morning, thank you.

These are my disclosures. I have no funding on amyloid research. I have consulting agreements

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unrelated to amyloid that are listed here, several license patents and some lectures unrelated to amyloid.

The WMIS, the World Molecular Imaging Society, is a nonprofit organization. Its membership is open to all persons and organizations interested in molecular imaging. There are corporate members, including General Electric, Siemens, Abbott, now Lilly, among others, and industry grants are part of what has supported WMIS in addition to their membership in meeting revenues. Importantly,

the World Molecular Imaging Society sponsors the National Oncologic PET Registry with the American College of Radiology. WMIS has about a thousand members, it focuses on molecular imaging and multimodal imaging. It was formed through the merger of the AMI and the SMI, so particularly the AMI, Academy of Molecular Imaging, was involved for many years in supporting CMS efforts to improve evidence for covering PET. And again, the National Oncologic PET Registry under AMI sponsorship was established in 2006, and currently the WMIS sponsors the NOPR 2009 and the sodium chloride

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NOPR registries.

I will skip this slide, I think you will all be happy about that, I think you all know that Alzheimer's is important, and I think you all know beta amyloid is important by now. Again, I prepared these slides in December. As an example, frontotemporal versus Alzheimer's disease is an important diagnostic issue. We've heard some of the challenges in management, but I just wanted to point out in this slide, which Kurt Frey was nice enough to give me, what we see here is the clinical consensus classification and molecular imaging classifications of Alzheimer's disease, diffuse Lewy body disease and frontotemporal dementia. What would ideally be true is if clinicians and imaging tests agreed perfectly, was that there would be no boxes like this, all these would agree. But what we see is there are a lot of instances, about a third, where the clinical diagnosis and the molecular imaging classification differ, so I think this supports the view that has been clearly shown, that clinical exam, though incredibly useful, is not the same as a molecular imaging that is based

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on phenotyping in the diagnosis of dementing diseases.

So, the WMIS supports Medicare coverage of beta amyloid PET under specific conditions of guidance. We believe that this is a reasonable and necessary approach for an FDA-approved agent. We believe that the data shown has shown a positive impact on physician and clinical decision-making and we've seen a number of indices of that today. And many of these points have been covered, the improved diagnostic accuracy, better differentiation, shorter ambiguity, facilitation of earlier and more appropriate treatment or nontreatment.

And I think how an imaging test is deployed, we want to know why for an FDG-PET, and think an appropriate use is essential, and I think the SNMMI/AA draft, or now criteria for appropriate use are ones we support, and this includes when it is appropriate to use it and when it's inappropriate, and I think avoiding inappropriate use is essential, and I think that these points have been covered, and just to keep us on time, I won't emphasize the WMIS agreement with these criteria.

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Now, I think that very clear criteria have been defined by the SNMMI/AA appropriate use criteria, but it's possible that there are additional clinical situations that may arise in which coverage is important to help make decisions, and the WMIS wanted to make it clear that should CMS want additional evidence, we're prepared to assist CMS in developing and administering registries for the collection of practice-based observational data from Medicare beneficiaries. Thank you.

DR. REDBERG: Thank you very much, Dr. Wahl. Next is Dr. Richard Frank, Frank Healthcare Advisors, and he is representing the Medical Imaging Technology Alliance.

DR. FRANK: Thank you. I'm a paid consultant to MITA and have no other conflicts. Like most people in this room I have personal experience with Alzheimer's disease; indeed, my mother and aunt both died of Alzheimer's, and each of my six siblings has participated in the DIAN study. We know what it's like to wonder for years about our mother's diagnosis as she faced difficult decisions which by the time her personal safety required that those decisions

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be made, she was no longer capable of participating.

MITA appreciates CMS participation in a series of workshops we have been conducting on clinical evidence and coverage, and we're grateful that CMS has granted our request for reconsideration of the PET national coverage determination, in which requests we proposed that novel PET agents and procedures in oncology, neurology and cardiology should be covered with immediate effect from FDA's approval of labeling.

Our request was based on three main ideas, each of which is applicable to today's deliberations. One, that PET has matured as a modality technologically, scientifically and

clinically during the 20 years since the original NCD. Two, that as distinct from nonproprietary agents like FDG, proprietary agents are developed with image reconstruction software and training to ensure quality images and interpretation. And three, that FDA's review of dossiers for PET agents is much more sophisticated.

Indeed, we support coverage with

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immediate effect for beta amyloid imaging, and we believe CMS can responsibly assign coverage determinations to local Medicare administrator contractors. This is warranted primarily by, one, evidence of sensitivity and specificity for the detection of beta amyloid as presented by the requester. Two, the rigorous regulatory process, including recommendations by an advisory committee for the beta amyloid tracer are currently approved by FDA. And three, a body of clinical evidence regarding other agents in this class, a good body of evidence that was deemed sufficient for the task force of qualified experts to publish appropriate use criteria in the Journal of Alzheimer's and Dementia.

Two of the three uses are particularly relevant to the Medicare population, mild cognitive impairment and possible Alzheimer's disease. The patient population was also carefully defined as those with objectively confirmed cognitive impairment but of uncertain diagnosis despite examination by a dementia expert and with expectations of an increase in diagnostic uncertainty and alteration in

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management.

These uses are within the scope of labeling for the currently FDA-approved agent, and therefore we endorse coverage based on the likely impact as noted also in the aforementioned publication. That is, one, change in medication management; two, change in ordering other tests; and three, the value of knowing.

The task force also listed seven uses for which amyloid imaging would be inappropriate and MITA endorsed omitting these from coverage.

Coverage with evidence development should be invoked for uses outside the approved labeling and for which evidence is suggestive but inconclusive. One example identified by the task force under the heading further

research questions is prognosis in healthy individuals and patients with MCI. Beta amyloid imaging detects a key pathological finding while the patient is still alive to benefit, thereby contributing to changes in intended management by increasing physicians' confidence in their ability to

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differentiate among the various pathophysiologies of dementia by ruling out AD if beta amyloid is below the limit of detection. To be clear, coverage should be established for beta amyloid imaging based on the clinical evidence demonstrating impacts on intended patient management decisions and physician confidence therein. The questions deliberated by the panelists today should focus on these two endpoints as appropriate for diagnostic procedures. Instead, the questions which have been put to the panelists will prejudice today's deliberations by seeming to hold this diagnostic procedure to inappropriate standards, that is, standards suitable for therapeutics. This ignores the fact that the purpose of a diagnostic intervention is different than the purpose of a therapeutic intervention. Diagnostics are used to resolve diagnostic dilemmas in part by ruling out disease, such as common end chest pain to rule out MI. Diagnostic intervention may result in watchful waiting or such as we've learned from the NOPR

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data regarding full-body PET CT, may result in the patients even declining therapy which is likely to be futile, thereby saving themselves unnecessary exposure to the risk of adverse effects and saving the system exposure to the cost, both of which we know are greatest in the waning moments of a cancer patient's life.

DR. REDBERG: 30 seconds.

DR. FRANK: In conclusion, we welcome the appropriate use criteria published by the task force since they are the result of a comprehensive review by domain experts. These uses are supported by ample clinical evidence, they are recommended in a clearly defined population within the CMS demographics and they have clinically relevant impact, and therefore are reasonable and necessary and should be covered. Thank you.

DR. REDBERG: Thank you, Dr. Frank. Next is Dr. David Kuhlmann, who is a

neurologist and sleep medicine expert from Bothwell Regional Health Center.

DR. KUHLMANN: My name is David Kuhlmann, I'm a board certified neurologist. I have no financial or other conflicts of

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interest. The goal of my talk is to cite recent research germane to each question posed to the panel members. I will also talk about concerns about the future direction of Alzheimer's care. For the sake of time I'm going to skip over the current NCD 220.6. 1.A is the most important question and that's the reason why I'm here. As Dr. Pearson from the ICER had mentioned, no study asked whether patients do better as a result of treatment. I'm just going to skip to florbetapir. What do we do when the test is negative? While beta amyloid on autopsy may confirm the diagnosis of Alzheimer's disease, it is not known whether beta amyloid is the cause of all cases of Alzheimer's disease, or even the cause of symptoms. According to Amyvid's safety information, a negative scan does not preclude the development of brain amyloid in the future, and that's according to Amyvid's safety information. If the test is negative, it doesn't rule out the presence or development of Alzheimer's disease. If the test is positive, a positive Amyvid scan indicates moderate to frequent

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amyloid plaques are present. An amount of amyloid plaque is present in patients with Alzheimer's disease but it can also be present in patients with other types of neurologic conditions and in older people with normal cognitions. That's according to a recent article. If the test is positive, it does not confirm Alzheimer's disease. Cost is well known. I'm recommending denying reimbursement for florbetapir testing because for Alzheimer's disease research there are already many federal agencies that provide that funding. By voting against reimbursement for florbetapir testing, CMS resources would remain focused on the management of the patient with Alzheimer's disease.

Now I'm going to go back to the questions, Question 1.A. How confident are you that there is adequate evidence to determine whether or not PET imaging of brain beta amyloid changes health outcomes for patients

who display early symptoms or signs of cognitive dysfunction? I would say it's low confidence. There's never been a study that

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has asked whether patients do better as a result of the florbetapir testing. This is referring to the Institute for Clinical and Economic Review, as Dr. Pearson mentioned earlier.

And then, I'm sorry, Question 2.A, how confident are you that there is adequate evidence to identify patient characteristics that predict improved health outcomes of patients who undergo PET imaging for beta amyloid? The scan has not been shown to be useful in predicting the development of dementia or any other neurologic condition, nor has usefulness been shown for monitoring responses to therapy, and this is according to a recent article in the New England Journal of Medicine.

So in conclusion, some are arguing that the indication for florbetapir is to scan to define whether someone has Alzheimer's, and when another scan after initiation of amyloid therapy is showing removal of cortical amyloid, proving efficacy of the medication. They equate a decrease in the amount of beta amyloid as proof that anti-amyloid therapies are

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working. They are treating the scan and not the person. They argue that if they can initiate the therapy preclinically they might be able to halt progression of the disease, but how does that help patients with suspected AD for which they are currently seeking the indication for florbetapir testing?

My big fear of anti-amyloid therapy is that they will show only marginalized disease but will be given FDA approval because, well, we really don't have anything else that's very effective in Alzheimer's. Patients with and without symptoms in their mid 50s will, as I saw in previous presentations, be screened with amyloid PET scans. These patients with scans that show beta amyloid will be started on anti-amyloid therapy even though 30 percent of cognitively normal adults have positive amyloid findings in the brain.

DR. REDBERG: 30 seconds remaining.

DR. KUHLMANN: So people who are started on these anti-amyloid therapies will be forever on these medications. Why? Because if they remain cognitively normal, the doctor will

tell them it's working and we'll continue on
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therapy, even though therapy may not be the reason why their cognition remains normal. If they start to have memory impairment the doctor will tell them, well, imagine how much worse it would have been without the medication, and they will continue on the therapy even though the drug may not be helping at all.
I'm fearing a shift in Alzheimer's care dollars from the payment for the prevention and management of patients to the payment for diagnosing patients for the purpose of future research. This is in strict opposition to CMS authority 42 CFR 410.32, which states that the ordering of a diagnostic test be used for the purpose of treating a beneficiary who uses the results in the management of the beneficiary's specific medical problem, and our goal in preventing preclinical Alzheimer's cases was not to change the actual beneficiary's development of disease, but to make this country great, and to whom we are all indebted.
DR. REDBERG: Thank you, Dr. Kuhlmann. Our next speaker is Dr. Michael Devous, a professor of radiology, and director of the
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Neuroimaging Core for the Alzheimer's Disease Center and North Texas Traumatic Brain Injury Model System, and associate director of the Nuclear Medicine Center at the UT Southwestern Medical Center.
DR. DEVOUS: Thank you. I have received research funding and honoraria from all of the manufacturers of anti-amyloid drugs and amyloid diagnostic agents, and by virtue of that have considerable experience with the use of amyloid imaging in patients with cognitive impairment as well as in the study of an aging brain. However, I'm here today as a private citizen at my own expense to speak to you both from my professional experience and from my contact with patients and their families directly affected with Alzheimer's disease.
In speaking with patient caregiver groups about amyloid imaging I hear heartbreaking stories of the consequences of incorrect or uncertain diagnoses, and heartwarming stories of the incredible relief and value that an amyloid scan has provided by yielding greater diagnostic certainty.
You've already heard a great deal
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about what a remarkable asset amyloid imaging is in the assessment of patients with cognitive dysfunction that might be a consequence of AD. There is a significant unmet diagnostic need that amyloid imaging can address by helping provide a definitive diagnosis with a detailed clinical evaluation and neuropsychological assessment, and current laboratory and imaging studies cannot.

These circumstances have serious consequences. An unclear diagnosis may lead to unnecessary or invasive tests that incur both more risks and more costs than PET scans. They hamper clinical decisions on management and prognosis, and hinder the patient's physician from either supporting that patient with a decision to continue working, or to begin the transition to disability, often entered because patients typically present at an early stage when employers and insurers might otherwise suspect a psychiatric basis for their complaint.

Amyloid imaging could play a major role to establish the patient's diagnosis and provides what he or she will need to plan their

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life. Life planning is a critical demand that must play a role in your decision. Amyloid scans significantly enhance diagnostic certainty about the likely cause of a cognitive impairment, which taken together with other clinical data afford patients and their families opportunities for well informed life-altering decisions not accessible without this information.

Early diagnosis when patients get more intact cognitive function lets them give input into their future care and end of life issues, including decisions about living arrangements, financial and legal matters, accessing support services, and employing critical support networks.

Finally, there is a very positive effect of this diagnostic opportunity on national health care costs. Even though there are no treatments to cure or prevent the disease, available treatments can help slow the progression of symptoms. Early interventions and good planning can reduce health care costs which would ensue when a sequelae of misdiagnosis or even no diagnosis are allowed

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to unfold. Staving off the disease by even a few months, which symptomatic treatments can

accomplish, leads to tens of thousands of dollars in savings on assisted living or nursing home care for each patient. A negative scan may lead to even more savings by guiding patients and their doctors to correct diagnoses and associated improved treatment, and by preventing treatments, hospitalizations and overzealous nursing home admittance because of this diagnosis of AD. Our country recognizes the urgent need and moral responsibility we have to address the Alzheimer's disease epidemic. CMS must continue to fulfill its mandate of making available new medical technologies that are reasonable and necessary for the diagnosis of cognitive impairment, including AD. Amyloid imaging represents a critical opportunity to do so within the CMS existing NCD process. Specifically the unmet need of increasing AD diagnostic accuracy combined with clear evidence of the benefits of a more accurate diagnosis and altered treatment plans for these patients make coverage of amyloid imaging a

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reasonable expectation for Medicare beneficiaries. I'll close with a brief note I received from a colleague in neurology. He wrote, I recently saw a 50-year-old woman with two master's degrees who presented with a one-year history of progressive memory loss, leading to the loss of her teaching position. There was no family history of dementing illness, MRI showed diffuse cortical atrophy, psychometric testing documented her memory dysfunction, but none of these tests was conclusive as to the underlying cause. She then had a positive amyloid scan. The benefits of this positive scan in providing an answer to this patient and her family cannot be denied. Appropriate medications and other supportive therapies have now been started and the family is in a much better position to plan for the future. This is a health outcome. Real people need real help, and we have a chance to provide it. I urge you to approve access for beneficiaries to amyloid imaging. Thank you.

DR. REDBERG: Thank you, Dr. Devous.

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Our final public speaker of the scheduled speakers is Dr. Teng Ong, who is the interim head of global affairs at GE Healthcare.

DR. ONG: Good morning, and thank you

for the opportunity to present. My name is T.J. Ong, global head of medical affairs at GE Healthcare America, a salaried employee. GE Healthcare provides expertise in medical imaging and has a broad range of diagnostic products and services that enable health care providers to offer patients earlier and more accurate diagnosis and treatment of cancer, heart disease, neurological diseases and other conditions that threaten the quality and length of life. GE Healthcare is the manufacturer of flutemetamol, an investigational amyloid imaging PET agent in clinical development for the visual detection of beta amyloid in the brain of adult patients with cognitive impairment who are being evaluated for Alzheimer's disease or other cognitive issues. A new drug application, NDA for flutemetamol is currently undergoing a rigorous regulatory review by the FDA. If and when the NDA is approved, we believe that there should be

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coverage with immediate effect per the FDA-approved label indication. Amyloid PET imaging would enable detection of a key pathological feature of Alzheimer's disease while the patient is still alive and may be able to benefit from clinical decisions made on the basis of such information, rather than at autopsy when a postmortem diagnosis is made and it is too late.

Amyloid imaging may enable physicians to rule out Alzheimer's disease in patients based on a negative amyloid scan in addition to clinical information, potentially helping physicians differentiate the physiology of dementia. This may provide a more accurate clinical diagnosis. This information may contribute to the changes in patient management with potential benefit for patients, their caregivers and families.

For a diagnostic tool such as amyloid imaging, we think that coverage should be established based on clinical evidence demonstrating impact on the intended patient management decisions and physician confidence.

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The Society of Nuclear Medicine and Molecular Imaging and the Alzheimer's Association recently assembled a task force to review the clinical evidence for amyloid imaging and to develop possible appropriate use criteria and recommendations for the clinical use of human

amyloid imaging to determine the presence or absence of amyloid in the brain. At this stage these criteria are suggested in a limited population based on the amount of clinical evidence published to date. Nonetheless, at GE Healthcare we endorse the appropriate use criteria which we believe should be reflected in a revised CMS coverage policy for the beta amyloid imaging. Thus, in order to provide patients and providers to this innovation that may help inform a treatment plan, we recommend that CMS allow coverage linked with provisos for the use in these defined subpopulations or clinical scenarios. In closing, GE Healthcare appreciates the opportunity to continue to work with CMS and other amyloid stakeholders in imaging to help inform this critically important area of health care policy. Thank you.

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DR. REDBERG: Thank you, Dr. Ong. Next we have two public speakers who are not scheduled, they have one minute each, and I just would like to take a moment to remind all of the speakers and the panelists to speak into the microphone so that those who are listening via webcast can hear you clearly. The first nonscheduled speaker is Rathan Subramaniam.

DR. SUBRAMANIAM: Thank you for the opportunity to speak. I'm Rathan Subramaniam, I'm a neuroradiologist and a nuclear medicine physician from Hopkins, and I'm speaking on behalf of the American College of Radiology as the vice chair of the Commission on Nuclear Medicine. We have more than 24,000 members and we support national coverage for brain amyloid PET imaging. Let me take and say as a health policy expert there are two focal points to improve quality, decreasing variation and improving appropriate use. Our goal is decreasing variation. We have with the American College of Radiology and the American Society of Neuroradiology set up a guidelines committee

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and I chair that committee, and we have come to early consensus about the training regimen, the CME and the continuous skill maintenance for interpretation of amyloid imaging to decrease the variation in the interpretation if it exists. We have the capacity at the American College of Radiology, we have trained more than 5,000 radiologists and nuclear medicine

physicians in various modalities --
DR. REDBERG: Thank you, Dr. Subramaniam. The next speaker is Lou Bordicco, and you have one minute.
MR. BORDICCO: My name is Lou Bordicco, and I'm an early stage advisor for the Alzheimer's Association. I guess I'm your anecdotal evidence in the midst of all this hard data.
I was diagnosed with Alzheimer's dementia at the age of 57 and that was after several years of diagnostic assessments, and I was diagnosed prior to the biomarkers and the amyloid criteria. Therefore, there was a mixed message, a mixed diagnosis, and this all left me with a lack of definition in my life, it left me pretty anxious, fairly confused and not

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having a sense of closure, which may have a lot to do with my being a high J on the Myers-Briggs inventory, but I definitely needed to have some closure, so I was unable to move on with my life and it delayed me from applying for Social Security disability and subsequently Medicare coverage as well, so I couldn't plan for the future. And having this imaging technology replaces, for me at least, doubt with certainty, and it helps me to engage services, and the medical management would have begun a lot sooner, I believe, so I therefore support the Medicare coverage for this technology. Thank you.
DR. REDBERG: Thank you, Mr. Bordicco, for sharing your story.
We now have the period for questions to the presenters, so I want to invite all of the presenters to take the open seats in the front row, and I want to invite the panelists to ask questions, speak into the microphone, and the first question will be from my vice chair, Dr. Sedrakyan.
DR. SEDRAKYAN: In reviewing the appropriateness criteria, certainly the three

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cases that you outlined, the committee outlined in the most recent publication, and certainly the third appropriate use criteria is not applicable to the CMS populations for younger patients, so I guess a lot of the discussion will be focusing around the first two appropriate use criteria as outlined in that publication.
The first question I have is how often do you treat patients with mild cognitive

impairment right now if they don't have substantial symptoms? And the second side of that question is, can you confirm that treating an amyloid-negative patient with dementia symptoms with Alzheimer's drugs is potentially harmful, or are there alternative therapies that are more effective? I can clarify the question if you need.

DR. FILLIT: Howard Fillit. I have been taking care of Alzheimer's patients for almost 35 years, and I can tell you that the patients that I see now are predominantly MCI early stage patients where the diagnostic evaluation is much more difficult because of the lack of certainty, and I think the PET has

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a lot more value in that population, and we could go into details. But basically these are people that often don't have functional impairment, that have clear memory problems, and diagnosis is very often unclear. As I mentioned, sometimes 50 percent of these people can revert back to normal and, roughly speaking, 50 percent will go on, and the only test that you really have at this point is the test of time, which is not adequate for most people.

I just wanted to comment on one thing that you said, that the third criteria doesn't affect Medicare, and I just want to point out, having had some managed care experience, that I think Medicare policy on payment has a very strong influence on how commercial insurers' coverage goes also. And so I think that whatever decision you decide today will have an impact on commercial insurers that insure the younger people that are not Medicare eligible.

SPEAKER: I had a question on the MCI population. What is the age range?

SPEAKER: Most of the people that I see in consultation are people in their 60s and

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early 70s.

DR. JACQUES: For the benefit of the person who's transcribing the transcript, although we can see who you are, please make sure, one, that you repeat your name whenever you're the new speaker, even if you have done it before, and please remember to speak directly into the microphone. Thank you.

DR. FOSTER: Norman Foster. I wanted to answer the question of whether we treat people with mild cognitive impairment, and the answer is yes, we always treat people with mild

cognitive impairment, that's why they come to see us. It may or may not be, depending upon the situation, but medications for Alzheimer's disease, there are often many other medications, and more frequently actually discontinuing medications, so knowing what we're treating affects our decision-making in patients with mild cognitive impairment.
DR. SEDRAKYAN: Can you answer the follow-up question, if treating patients who are amyloid-negative will have harms associated with that if they get treated with Alzheimer drugs?

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DR. FOSTER: So, it does not always -- it's not always true that they will get noticeably worse if they're treated with Alzheimer's drugs, but often the kinds of medications differ. For example, in patients who have apathy and they have Alzheimer's disease, then we treat for depression, because that's the usual explanation. In patients who have apathy with frontotemporal dementia, we do not treat with depressive drugs because it causes a brain disease instead, so it makes a huge difference.
DR. SADOWSKY: Carl Sadowsky. I think there are probably almost ten million Americans now with a diagnosis of mild cognitive impairment, probably twice as many as we see with Alzheimer's disease, which is probably a little over five million. We know from the trials presented today, and there may be a little confusion in the Doraiswamy trial. In that trial the number of patients who deteriorated and the amount they deteriorated was almost six points on the EOS. That's a massive deterioration in a patient with mild cognitive impairment with a positive amyloid

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scan. With a negative amyloid scan the patients actually improved a little bit. So you can't only look at conversion, you look at the quantitative deterioration. So amyloid is bad for the brain. When patients deteriorate, as a clinician you're sitting there all day long seeing these kinds of patients. It's so valuable not to be treating people who don't have pathology and treating people who do. We certainly don't want to put amyloid-negative patients on cholinesterase inhibitors with potential side effects. Even normal patients with amyloid in the brain do worse than normal patients without amyloid, so

being able to discriminate is tremendously helpful to the clinician.
DR. REDBERG: Dr. Fendrick and then Dr. Gutman.
DR. FENDRICK: I'd like to make two quick comments while I direct a question to Dr. Aisen, please.
Just quickly, one is, sitting on MedCAC for a number of years, the more case studies I hear as opposed to large trials makes me nervous. We heard an awful lot of case

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studies and anecdotes, as we heard specifically from our last speaker. A lot of you have spoken about the idea of limiting coverage decisions to targeted populations, and again being a generalist and not an expert in the field as you all are, we have seen so many examples of lung volume reduction surgery, PSA testing, vertebroplasty, coronary stents, that have not done that.
But my question is, my concern in studies for new innovations for Medicare is the idea of not the first test but the multiplicity of testing that we see over and over and over again. Can you tell me a little bit about whether a negative means a negative, or does my patient just come in and want to get tested every year for every single thing, and this will not be the case in amyloid every time they forget their keys?
DR. AISEN: In the case of amyloid testing for AD when someone has a negative scan, we can now say with confidence that we have no concern about Alzheimer's disease for about 10 to 15 years.
DR. FENDRICK: So how could we know

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that, given that we haven't been able to follow populations for that amount of time? You're looking backwards, right?
DR. AISEN: Well, I'm saying that the predominance of the evidence, for example, the curves using either autopsy data or amyloid imaging data, or the careful biomarker data in familial AD, they all have demonstrated a 15-year gap between the appearance of amyloid in brain and the onset of symptoms.
DR. REDBERG: Okay. I just note, what you said seems to be conflicting with what some of the other testimony we heard said, as well as the FDA label, which states that there's a reduced likelihood, but that a negative scan does not rule out Alzheimer's, and I hear you

saying it does for 10 or 15 years, so I'm wondering what you're basing your statement on.
DR. AISEN: Sure. The absence of amyloid is inconsistent with the diagnosis of Alzheimer's disease. Is the test perfect in sensitivity and specificity, no, but as you heard, the test is in the mid 90s for sensitivity and 100 percent for specificity, so it's highly accurate for the demonstration of

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amyloid. The absence of amyloid is not consistent with the diagnosis of Alzheimer's disease, so a negative scan is highly accurate not only for the time at which the scan is done, but for the subsequent 10 or 15 years, since Alzheimer's disease cannot occur with the absence of amyloid.
Now amyloid can occur, say three years or five years later, but the gap between the first appearance of fibrillar amyloid based on, again, both autopsy and amyloid study, and the presentation of the dementia syndrome is such that a negative scan is highly informative for a decade.
DR. REDBERG: Thank you. Dr. Gutman.
DR. GUTMAN: In these guidelines there are three populations, patients with persistent or unexplained, MCI patients with dementia with atypical presentation, and patients with atypical age of onset. Is there actually any evidence in these three populations that the test works? The fellow who presented the FDA findings, the FDA findings were very small, 59, and there were actually 75 percent of patients who were either cognitively normal or had AD.

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So my question is, has anybody actually studied patients in these categories to demonstrate that there is performance? You know, in that somewhat enriched population there was spectacular sensitivity and specificity, but what I'm asking is do you believe that that population will match these particular intended uses, or is there a possibility that they may not and performance may slip? And although not addressed by FDA, in the packet we received there's this French finding using clinical diagnosis as an endpoint that would suggest that the performance is perhaps not quite as good as what FDA found.
DR. MINTUN: I'm Mark Mintun. So, it's a good question to say is this population a valid population, and I guess there are a couple different ways. One is that it did

image a wide spectrum. I mean, there were half of the people did not have Alzheimer's disease, did not have symptoms, and yet they had various pathology when they died. Half of them had various degrees of amyloid pockets, there was a whole spectrum of amyloid intensity essentially seen on pathology. So the test was validated

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over a very wide spectrum of amyloid pathology. So you can start thinking, well, what about the concept that these were end of life patients, maybe there was something different about them. Well, one of the things that the FDA asked us to do is to look at -- obviously it's very hard to get pathology from people who are not end of life, but they did indeed pursue that same thought you had and said what if the test doesn't perform as well and you cannot get reliable interpretations from a different population?

So they actually asked us to look at mild cognitive impairment, include that in our reliability studies with the possibility that that might actually be a harder scan to read, and indeed, actually it turns out that -- and it looked like our ability to reliably read those scans actually was the highest, and we believe that that had to do a great deal with the fact that an end of life population is actually a very difficult population to scan. These are people who are ill, have trouble cooperating with the scan, it was amazing, their altruism to be able to volunteer for the

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study in the first place. But I think it's actually also very hard, you know, I think it actually is one of the hardest cases to be able to read.

So we think that all the evidence, when you look at carbon-11 PIB where thousands of scans are done and track incredibly well with both ApoE4 risk factors, with CSF, you saw the data presented by Randy Bateman that it's amazingly good at tracking with other biomarkers, and then at the same time being able to be predictive. All of those things indicate that from normal, essentially patients that have no symptoms to patients at end of life, there has been no evidence that this test is not measuring amyloid and reporting it faithfully.

DR. REDBERG: Dr. Faught and then Dr. Mock.

DR. FOSTER: My name's Norman Foster,

may I answer that question also? It's very important to see in the second criteria that these are atypical spaces, and what I would refer to as the same series Dr. Mintun talked about. These are not people that simply had

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Alzheimer's disease or did not have Alzheimer's disease, but they also had other neuropathologies. So what we were able to identify is amyloid pathology in the presence also of other pathologies such as stroke, which is very common.

DR. GUTMAN: But the selection criteria for at least the FDA study wasn't based on pathology, it was based on end of life.

DR. FOSTER: That's correct, and so there was also, not only was there a wide degree of amyloid pathology, but also there was a wide range of other pathologies.

DR. GUTMAN: But there were only a handful of MCIs.

DR. FOSTER: I'm not addressing the MCIs in that case, you're right.

DR. FAUGHT: I'm Ed Faught, I have a couple, a comment and a question. We've heard a lot of discussion about the positive benefits of being more certain about diagnosis. I'm a little concerned about the effect on a false positive. If 20 or 30 percent of elderly people have cerebral amyloid, what's going to be the impact on those people when they get

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positive scans? Do they quit their job, depression, suicide? Because I'm afraid this test is going to be equated with a diagnosis of Alzheimer's disease, so that's the question.

DR. FOSTER: Norman Foster. These are not false positives. These are not patients who have Alzheimer's disease, which is a difference. The scan is not proposing to say whether somebody has Alzheimer's disease or not, or Alzheimer's disease dementia. They're proposing to say that they have amyloid deposits.

DR. FAUGHT: I absolutely agree with that, but we've heard that it's almost equivalent, and that's a concern in terms of when it gets out in the general population.

DR. FOSTER: That's fine, and the appropriate use committee --

DR. FAUGHT: That brings me to my next question. The appropriate use committee stated that this needs to be applied to people who have objectively confirmed impairment, I heard

that phrase, documentation of clinical decline, clear memory problems. How is that going to be defined? When I fill out a request to get this

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scan, what am I going to have to prove that the patient is indeed having memory problems, a neuropsychology test?

DR. FOSTER: These also follow the already existing CMS guidelines for the use of FDG-PET, in which there is not only an expert reader of the study, but also an expert who incorporates that into clinical decision-making. And for documentation, there are many things that can be used; neuropsychological testing, for example, is required for coverage of FDG-PET so that may be the case. Does that answer your question?

DR. FAUGHT: Well, it does, although I assume that some of the arguments for this modality is that it would reduce the use of extensive testing like neuropsychological testing. Are you suggesting that may not be the case?

DR. FOSTER: As in my second case in my materials, or third case, I guess it is, often we are now forced to watch patients with serial assessments, both clinical and neuropsychological, to decide whether there's a presence of Alzheimer's disease. So in that

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example, you can see that perhaps neuropsychological testing, repeated neuropsychological testing to document progressive decline is needed.

DR. FAUGHT: Thank you.

DR. REDBERG: I have next Dr. Mock, then Dr. Lyketsos, then Dr. Cozzens. Did you want to make a comment?

DR. KUHLMANN: David Kuhlmann. And you made me think about what I was unable to do in my presentation because of problems with my Power Point. I don't know if you saw the article by the New York Times on November 15th. It was talking about someone who was diagnosed as a true positive for Alzheimer's disease. But I've heard a lot of talk about how people are somewhat relieved finding out that they have an accurate diagnosis. Well, this is a quote from the article. The Jimenezes have struggled ever since to deal with this devastating news. They are confronting a problem of the new era of Alzheimer's research. The ability to detect the disease has leapt far ahead of treatments. There are none that can

stop or even significantly slow the inexorable
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progression to dementia and death. It also mentions in the article how you can be, if you have a scan that's not, is a pre-cover entity, how some health insurances may be able to use that against you in determining funding. And Dr., or Mr. Jimenez states at the end of the article that he kind of wishes that he wouldn't have even had the scan to begin with.
DR. REDBERG: Next -- we have a number of more questions. We have a hard stop at noon so I'm trying to get three questioners possibly before noon, and then we will get to the next session. So Dr. Mock and Dr. Lyketsos and then Dr. Cozzens.
DR. MOCK: Yeah, Curtis Mock. I don't have anyone singled out to answer, so please offer up. I really have three questions I'd like to outline. One of the things I want to ask you to address is the certainty that's been discussed today in the determination of diagnoses, and help me understand how 30 percent of the elderly with positive amyloid scans that have normal cognitive function can be providing certainty in this discussion.
The second is, the whole conversation
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about adding additional certainty by the scan, really, is this a therapeutic modality or is this a diagnostic modality? Second, I want to have someone really talk about outcomes, please. You are the experts in the field. Help me understand the studies that have been done that have shown outcomes and improved quality of life, and I've heard so many people refer to costs here. Please guide me to the studies that have shown reductions in cost because of PET amyloid scan.
And the third thing, I didn't hear anybody say that they're a lawyer, but I'm wondering about my patients and my family members that are going to get scanned that are going to have implications on the future of their coverage decisions for insurance and life and jobs. Is this cart ahead of the horse regarding beneficiary protections that should take place before this is widely spread?
DR. FOSTER: Norman Foster. Let me try to answer some of your questions. One of them has to do with how the performance of a scan might affect coverage. It will not affect health care or health insurance coverage, it
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might affect long-term care coverage. However, if somebody already who is scanned has significant cognitive deficits, then that itself also has a similar effect. Whether the scan is performed or not does not really make a difference in whether the patient has symptoms. All we're doing is identifying the cause of the symptoms.
And many of the things that you're talking about, including the recent article with Jimenez in the New York Times really is about the disease they have, or the symptoms that they have, rather than the performance of the scan.
DR. MOCK: I did hear mentioned today, someone elected to have a scan instead of an LP. And if I was one of the 30 percent in the elderly population and my scan was positive because I didn't want to have an LP, wouldn't that affect my opportunity for future employment?
DR. FOSTER: The scan should not be performed according to the appropriate use criteria in people who are asymptomatic, so I'm not advocating that that happens.

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DR. MOCK: Thank you. And next, please go ahead. I'm still looking for that discussion around proven outcomes and also beneficial from a cost perspective.
DR. AISEN: I just wanted to clarify an earlier question so I'm afraid I'm not going to address the cost. I think we've caused some confusion in our discussion, in part because the field is changing. 30 percent of clinically normal older individuals will have a positive amyloid scan. That's because 30 percent of clinically normal older individuals have amyloid in brain. Most of us, although probably not all of us, believe that they have the first stage of Alzheimer's disease, but that's not under discussion in the utilization criteria, that's still an area of research.
The utilization guidelines suggest that amyloid imaging be used for people who do have cognitive symptoms.
How would you identify those people? Not with neuropsychological testing, with an interview with an individual, with an informant, typically someone in the family, and a three-minute cognitive screening like an MMSE.

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That's how you identify people who have mild cognitive impairment or dementia syndrome, and

those are the people for whom amyloid PET imaging may be informative; if the diagnosis is unclear, it can be rendered highly clear with amyloid PET imaging.

As far as CSF versus amyloid imaging, a lot of the same information can be obtained through spinal taps, so there is a big problem with standardization and assay reliability in CSF right now which, you know, renders it less useful than PET imaging.

DR. REDBERG: Does someone want to address the outcomes question?

DR. SADOWSKY: Carl Sadowsky. So in the office you see a patient with mild cognitive impairment, and the scan is tremendously helpful to stratify those patients. As Bob Aisen said, a very simple evaluation for episodic memory loss is what we do clinically. Now, if you have a patient and you send him for a scan and it's positive, you don't need to do a detailed neuropsychological testing, you basically have your diagnosis. They have prodromal Alzheimer's disease, we

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know that statistically they're going to deteriorate, we would treat those patients aggressively, whether it be cholinesterase inhibitors or putting them in a clinical trial. In a patient with a negative scan, you could stop there. You might want to do neuropsych testing but you might not, but you're surely not going to put them on drugs like cholinesterase inhibitors. You might scratch your head and say are we dealing with depression or vascular disease. But it helps dramatically in terms of how much money you're going to spend because you go down two different pathways. In the old days, six months ago we were just guessing, and we were treating everyone if you wanted to be proactive.

DR. MOCK: Do we have any evidence on outcomes that has been developed?

DR. PEARSON: I was just going to -- Steve Pearson, sorry. I was just going to in a sense summarize part of what I said earlier. If and when there's a therapeutically effective agent, the tests that are used to identify the enrolled population will be judged as a

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de facto diagnostic test for treatment-responsive Alzheimer's disease. There almost will be a new way of thinking about it, there will be treatment-responsive Alzheimer's

disease, and there will be a set of diagnostic instruments that in a sense got you that population that was tested and showed a positive benefit.

We are not there yet, and so the arguments about outcomes related to testing are related to the value in terms of how it affects clinical decision-making and other testing for patients primarily who receive a negative test, I think most people would agree, because the positive tests definitely still remain more controversial in how they should be applied to clinical decision-making, given that you could have a patient with dementia who has amyloid, but since 30 percent of cognitively normal elderly have amyloid, could it be true, true and unrelated. So that's why I think there has been a lot of discussion about value of knowing, planning and that kind of thing, and the best existing published evidence is the one Grundman article that looked at reported intent

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of management plans for patients, a single study that in my personal judgment raised as many questions as it answered about the potential benefit of the test.

DR. REDBERG: Dr. Lyketsos, I'm going to give you the last question before lunch, and then we'll resume and get to the rest of the questions hopefully in the hour after lunch.

DR. LYKETSOS: Thank you. I was struck by the comment Dr. Frank made about what the standard is for a new diagnostic in Alzheimer's disease, and I wanted to ask the question in relationship to the already approved use of FDG-PET by CMS and get a contrast between the two. Is this a better test of not, and should it not be held to the same standard that FDG-PET was held. So did FDG-PET, for example, demonstrate the kinds of outcomes that we're asking to see for amyloid imaging? And what is the evidence that compares the two to say that one is a comparable, better or worse test than the other for the purposes that we're talking about?

DR. AISEN: FDG-PET and amyloid PET are apples and oranges. FDG-PET is giving you

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a general pattern of synaptic function that has not proven to be reliable as an indicator of underlying pathology. Amyloid PET is molecular imaging and is highly reliable as an indicator of underlying pathology.

And I just wanted to address the point

of the 30 percent of normals have amyloid. Again, that's not actually accurate. If we're talking about the accuracy of a positive amyloid scan of someone who already has symptoms, which is what we're talking about, the fact that 30 percent of normals are positive is irrelevant, that's not part of the same population. Those 30 percent of normals are going to develop into the symptomatic people later. Now, at this point in time the guidelines are suggesting that amyloid PET be used in symptomatic people, and we believe that in symptomatic people, if you have a positive amyloid scan, you have Alzheimer's disease. It's not a 30 percent false positive.

DR. FOSTER: Norman Foster. I have extensive research experience in both FDG and amyloid PET, so I wanted to address this issue. Imaging ought to be used to answer specific

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clinical questions, and whether to use FDG-PET or amyloid imaging depends upon what the question is, and the answers are different. So if the question is what part of the brain is affected, FDG-PET may be better than amyloid. Amyloid answers the question about pathology. I think that the experience with FDG-PET is a good example of how this might be done with amyloid PET.

DR, LYKETSOS: Let me just follow up, though. FDG-PET is now approved for the diagnosis of Alzheimer's disease.

DR. FOSTER: No, it --

DR. LYKETSOS: In the differentiation --

DR. FOSTER: It is used to differentiate Alzheimer's disease from frontotemporal dementia, and both have to be significant considerations.

DR. LYKETSOS: But just to stay on that if I could for a moment, that's one of the recommendations now for the appropriate use, is for the differentiation of Alzheimer's or other conditions. So would you say that in that context FDG or amyloid is better? In other

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words, are we holding amyloid imaging to a higher standard from a test that's already approved?

DR. FOSTER: Those specific studies have not been done. There are anecdotal reports of series showing that they may get different answers, so they may have complementary information.

DR. REDBERG: We're going to wrap up. I would like to just add as a clinician and a cardiologist, almost all of my patients that come in, and certainly in the Medicare population, are complaining about some issue with memory loss. So I don't know if that meets the criteria for mild cognitive impairment, but I'm just imagining that these patients, if they did have an amyloid scan that was positive, it would be a very, you know, something quite significant in terms of impact on your life, what you do and what you treat. So I would, when we return after lunch, like to hear a lot more about outcomes for patients, because as Dr. Pearson noted in the literature notes, we really don't have effective treatments right now for mild cognitive

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impairment or for Alzheimer's disease, and so that's what I would like to concentrate on when we return.

We do right now have an hour break for lunch, so we're going to come back at one p.m.

(Recess.)

DR. REDBERG: I want to welcome everyone back, and hope you have had a good lunch, and thank you, panel, for all getting back.

I said we will start with Dr. Cozzens' question and, as I said, I think there are a lot of questions, and I hope we'll get to a clinical focus. Thank you.

DR. COZZENS: So, my question is about costs. I'm a new member on the panel so I don't know how much I can talk about costs.

DR. REDBERG: Be sure to speak into the mic.

DR. COZZENS: I thought I was.

DR. REDBERG: That's better.

DR. COZZENS: I would like to talk about costs. How much does this cost, does this test cost? I mean, is it like a $10 test or is it a $20 or is it a $1,000 test? You

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know, if I do a rate of brain autopsy to look for amyloid, Medicare only pays me about ten bucks. How much are you guys getting for this? I see that there's no CPT code for this, that the CPT code you would have to use is an unlisted code. There's a CPT code for PET imaging for metabolism and there's one for perfusion but there's none for a diagnosis like this, so it would have to be an unlisted code, but I imagine the drug itself has to be paid

for, and I'm sure this all comes out of Medicare Part B too, so I mean, this is a major issue. How much does this cost.

DR. JACQUES: And actually, before he answers, let me just sort of clarify one thing, just so everybody is on the same page. With the exception of certain preventive services where the statute specifically instructs us to take a look at costs, CMS as a matter of policy does not in general consider cost in a coverage decision. That said, I am mindful that what we, we meaning all of us, what we may put in the bucket of costs actually represents things that happen to patients.

So, is it easier to talk about costs

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than to talk about a patient being readmitted to the hospital, a patient having an adverse event, a patient having a positive event? I mean, those are all things that people can debate. There is nothing that would prevent the MedCAC or your conversation from talking about cost, it's just that when we make a coverage decision, that's going to go off to the side. So it could be at some point informative for us if you do decide to talk about costs, if you could have some conversation about how that translates into a burden or benefit as experienced by the patient.

DR. COZZENS: Well, yeah, that's certainly part of it, and I think that there may be some unattended costs and cost savings as well that may be associated with it, because if someone is confirmed to have Alzheimer's disease, you send him off to the nursing home and no more treatments for anything else, so that may be something that would save costs.

But I'm still, I'm not an employee of Medicare so I can talk about costs, and I'm just curious, you know, if it's a $20 test,

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then why are we here? If it's a $3,000 test, that's a major issue.

DR. REDBERG: We're here about patient benefits, no matter the cost.

DR. MINTUN: One of the things that Eli Lilly can set is the wholesale cost, which is about $1,600 for the drug.

DR. REDBERG: Speak into the microphone.

DR. MINTUN: This is Mark Mintun. One of the things that Eli Lilly can set is the wholesale cost and that's about $1,600. That

cost is to the imaging center and the imaging center has to bill an insurance or payer of the patient. And so at that point, we don't control the cost from that point onward, and I can sort of ask other panel members if they have any ideas on this.
And then the other question you asked about CPT codes, I'm not a specialist in this area, so I want to apologize if I don't know, but it's my understanding at this moment, amyloid PET imaging does not have a CPT code, so I do not know exactly how that would proceed, and I assume that would be with

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conversations with the Agency.
DR. COZZENS: Well, since there's no CPT code, it's carrier priced, and so it's up to the local carrier to decide, I believe.
DR. REDBERG: Thank you.
Dr. Miskimen.
DR. MISKIMEN: Yeah. I wanted to clarify something about who will actually get this test. So, I am definitely reading the appropriate use criteria, which is definitely helpful. In the preamble, though, you talk about that this should be done for a diagnosis, as a diagnostic test, but when diagnosis is uncertain after a comprehensive evaluation by a dementia expert. In some of the presentations this morning it appeared almost as if some of these comprehensive evaluations, in addition to a clinical history and a mini-mental, would almost go down in the hierarchy of how you're going to be doing the diagnosis, specifically about preventable causes of the dementia. So how is it that that's going to be brought forth, is there going to be a little flow list that as soon as you want this test you're going to be able, then, to advise the doctor, have

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you done any PSH, have you done any B-12. Can you clarify that, because I'm not sure how that is talked about right now.
DR. THIES: Well, I apologize ahead of time, I'm not going to be responsive to the question. I have to address a couple of things that have gone on previously.
DR. REDBERG: Can we please stick to the question?
DR. THIES: I think this is something that really does require an address. We've heard people with the diagnosis of Alzheimer's disease being characterized as we put them in a nursing home and they get no other care.

That's frankly offensive to the Alzheimer's community, and it's contrary to many CMS directives, so I think that that ought to be perfectly clear, that that's not the state. The only other thing I would really like to address is there was an earlier question about the relationship of data in FDG-PET and what the bar for evidence is in this particular test. And the fact is that the FDG-PET discussion was starting from a background of the use of FDG-PET as a routine

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diagnostic for Alzheimer's disease, and the whole discussion was about how we might limit that to something that was more rational. We've already done that limitation as this discussion has come to you, so I think any idea that this test should come with a completely mature body of outcomes research would set a bar for CMS approval that really just doesn't fit with previous activities. I'm happy to let somebody else --

DR. REDBERG: Are you going to answer Dr. Miskimen's question?

SPEAKER: I would be glad to. I think typically -- and there's sort of a general consensus about this. The typical situation is you see a patient in the office, you do a careful history and physical, you come up with a working diagnosis that does not preclude the metabolic abnormality so it would not replace doing thyroid function testing, B-12, et cetera. Typically you want to do some sort of structural imaging, whether it be MRI or CT, and in my mind that's when you might want to consider amyloid imaging after that's done. The place where you're going to end up

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saving money is you might not want to do an FDG-PET, I do very few, for example, because I'm not really confident of the results that I'm getting. I think it would cut down dramatically on neuropsych testing if I had a clear diagnosis. But I think in the hierarchy as we stand now, it would be after a still fairly traditional workup.

DR. REDBERG: I'm going to ask a question and then go to Dr. Hartman-Stein, because I heard, if I wrote down correctly, I think Dr. Gandy said that once we saw amyloid it was kind of too late because the process was established. First of all, it's not clear to me that amyloid is a byproduct of whatever it is that causes dementia, there's no evidence

I've seen that says it's causative, and then that it was too late to start treating, because the process was established once we've identified amyloid. And if that be the case, then I'm wondering what is the value to the patient of establishing a diagnosis that is too late to start treating and actually make a difference.

And just getting to that, looking at

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the data for the current treatments for Alzheimer's disease, there are cholinesterase inhibitors which are said to make mild cognitive improvement in 30 to 40 percent of the people that take them that are not clinically significant, that have follow-up up to one year. So what are the positive benefits to this establishment of amyloid to patients?

DR. FILLIT: Howard Fillit. I have to say just at a certain risk, that I appreciate everyone's questions, I think they're really good questions, but, you know, for us, it kind of reflects to us on the panel, you know, a bit of a lack of knowledge of the process of Alzheimer's care and what we're all about, and I think there is an educational need here.

Let me just say in answer to your question that we have to distinguish between some of the research issues, the role of amyloid in pathogenesis, the possibility of having anti-amyloid therapies, those are all research issues, some day we might have therapeutics, but that's not the point of discussion here. The point of discussion here is purely whether or not this is a diagnostic

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test that would be of value in the care of patients.

Now I have a question for you all, okay? I have been practicing geriatric medicine for almost 35 years. During all of that time I have been taking care of Alzheimer patients, their loved ones, their caregivers, their families. The first drug was approved around 1995 by the FDA, four drugs approved, really five, because they're safe and they're efficacious. So, we hear always every day about therapeutic neologism in this disease. We have safe and effective drugs for this disease. I think the problem is that people don't know how to measure their effectiveness. But my question to you is, what do you think I have been doing for 35 years? My point is I have been taking care of people, and I

know of no chronic illness where we have a cure where early diagnosis doesn't play an important role in getting people into care management. The role of the physician is to take care of people. There are huge care management issues in this disease where early diagnosis has been shown to be cost effective, and so I think it's

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very important to realize the role of early diagnosis, particularly in this MCI window where early diagnosis is very difficult. If somebody walks into my office and they're demented in every way, yeah, I don't need a scan. But where the challenge is is in finding those people with MCI mostly who need a diagnosis, and I illustrated that, I think pretty well with some of my cases, where it really makes a difference to know what's going on, and you can get people in therapy or not. The lesson on cost is that this is the third most expensive disease in our society today after heart disease and cancer, $200 billion a year in direct and indirect costs. I've done a lot of health economics research and --

DR. REDBERG: Dr. Fillit, I think that we all agree that Alzheimer's is a terrible disease and we would all like to do everything we can to improve the care of our patients with Alzheimer's. I'm sure that's what you have been doing and that's what many doctors have been doing. The question before the committee is what evidence do we have that the beta

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amyloid imaging test is going to help us improve the care of our patients. That is the question I asked and I want to hear other panelists try to address the answer to that question that I asked. Thank you.

DR. SUBRAMANIAM: Rathan Subramaniam from Johns Hopkins, representing American Society of Radiology. I want to answer both the benefits and the outcomes using the CMS precedent. In 2005 we did not find FDG-PET CT for oncology for all cancers. Working with CMS, experts in the field set up a registry whereby over the last seven years we have shown that doing FDG-PET for almost all cancers except probably prostate changes management 35 to 36 percent of the time. That led to CMS approving FDG-PET CT for all cancers. Let me ask the same question for amyloid. Do we have evidence to link outcomes? Not to survival. Because outcome has two

levels, one is overall survival and progression-free survival, and the other is change in management. It's very hard to connect a test to outcome, but we can show it changes management. So what I think --

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DR. REDBERG: Okay. So we don't have data, you're saying.

DR. SUBRAMANIAM: Yes.

DR. REDBERG: Thank you very much.

DR. SUBRAMANIAM: Just survival, we have --

DR. REDBERG: I'm going to move on to the next question. Dr. Hartman-Stein.

DR. HARTMAN-STEIN: Paula Hartman-Stein. I'm a clinical geropsychologist and my primary patients that come to see me have MCI. Several of the speakers today have said that one of the potential benefits of this amyloid scan is then to negate the need for neuropsychological testing, and one person, I think Dr. Thies said that it's expensive and so, you know, we have to look at the costs, and I'm also looking at costs.

So I've done a little calculating this morning and the current -- I live in Ohio and CGS is our Medicare carrier for Ohio and I believe in Kentucky, you know, it's by region, and for the -- I'm not a neuropsychologist, I'm a geropsychologist. I do neuropsych testing and I do a lot of psychotherapy and health and

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behavior interventions, so I do the gamut and work with family members. Anyway, I figured this out. And now Doctor, is it Kuhlmann, in your slides you have that the cost is between three and six thousand dollars, and then we heard earlier that it was $1,600, so I don't know what it is, but does anybody have a more definitive, and then I'm going to go from there with my question.

DR. LARVIE: Hi, Mykol Larvie, and just to be definitive about this --

DR. HARTMAN-STEIN: Sure.

DR. LARVIE: The radiotracer is supplied to us at a cost of $1,725 per dose, and our total charge for the scan, all services included, is $3,000.

DR. HARTMAN-STEIN: Okay. So, is that approximately what it would be in the country, around 3,000 or something? All right, let's take that. Okay. If a person is seeing a psychologist for neuropsych testing today, 2013 rates, if you do five hours, you bill for five

hours, that means you see the patient about two-and-a-half to three hours, the total cost would be $540.92. And maybe you're going to do

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a little more, the average seems to be around seven units today, and that would be $633.64, to be precise.

Now, many of you in the room are physicians and know about PQRS, Physicians Quality Reporting System. Well, if you are doing PQRS as a neuropsychologist today, 2013, you have to do nine different measures in order not to be penalized, we all know that if we're in practice in 2015 we will be penalized if we don't comply with PQRS, and listen to this. So to do your neuropsych you have to do a staging of dementia, you have to do the cognitive assessment, you have to do a functional status assessment, you have to assess the neuropsychiatric symptoms, the management of those symptoms. You have to screen for depression, you have to counsel regarding safety concerns, risks of driving, and give caregiver education and support.

So I guess my question is when we look at costs and benefits to the patient, you're all saying well, you don't have to go through that. It certainly can be tedious, although some of us who have been doing it for 25 years

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try to make it fun and not so horrible, and most of my patients say, you know, that wasn't so bad. Anyway --

DR. REDBERG: Get to your question.

DR. HARTMAN-STEIN: The question is, what's the benefit, cost-benefit ratio between this test and repeat neuropsych testing?

DR. FOSTER: It looks like you're not giving neuropsychological testing enough credit, because the value is not, is much more than just coming up with a diagnosis. It's actually defining what the patient's deficits are and being able to do these other things, that's right. So as a physician, what I would do is order the test that's appropriate to answer the clinical question that's important for my decision-making, and I'm not one of those who advises eliminating neuropsychological testing just because I know there's amyloid in the brain, but those are different questions.

Neuropsychological testing cannot tell me whether there's amyloid deposits in the brain, which is part, an important part of

25 putting the entire context, clinical context
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1 together, so I don't think it's one or the
2 other.
3 DR. HARTMAN-STEIN: But there's been
4 people saying that the advantage of the amyloid
5 testing is that you don't have to do it as
6 much.
7 DR. FOSTER: Not all of us agree, and
8 I forgot to identify myself as Norman Foster.
9 DR. REDBERG: Dr. Mock's next, then
10 Dr. Sedrakyan.
11 DR. MOCK: Curtis Mock. I want to
12 reiterate something Dr. Redberg said about
13 appreciating the clinicians in the field. Dr.
14 Fillit, I also appreciate what you do for the
15 Medicare beneficiaries, as well as the other
16 clinicians across the country. It's critical,
17 it's important, and it only is going to get
18 more so.
19 I want to change gears a little bit, I
20 want to talk about two things that, one that
21 has been touched on and one that I haven't
22 heard anything about. The one that's been
23 touched on, I would like a little more
24 definitive input from the specialists around
25 quality of reading. I have heard that it's
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1 okay if you're interested to voluntarily take a
2 course, either on line or in person, but I
3 guess my question is, in light of this
4 discussion, is that really adequate? And what
5 are the plans for the industry to support that
6 moving forward?
7 DR. SUBRAMANIAM: This is Rathan
8 Subramaniam from the American College of
9 Radiology. We have set up a guideline
10 committee and the document will be finalized by
11 the committee next week. We have come to
12 nearly a consensus, how many scans someone
13 needs to read to qualify initially, and then
14 how many hours of continuing medical education
15 someone needs to have to initially qualify, and
16 then every year after, then how many scans
17 someone needs to read in every three-year cycle
18 to maintain the skill.
19 So, the reason why we have not
20 released it is because the committee is going
21 to finalize it next week, I'm the chair of the
22 committee, and then it goes back to ACR and the
23 American Society of Neuroradiology, those are
24 the two institutions organizing this guideline.
25 DR. MOCK: Thank you. With what's at
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stake as we've heard in discussion about the reading, the outcome of this scan, I would certainly hope that it wouldn't be elective, I would hope that it be a required educational process.
And that takes me right to my second issue that I wanted to address.
DR. MINTUN: This is Mark Mintun. It is actually in the label that the FDA has, it actually says that all interpreters of this scan should take a specialized training program, so the message that the FDA gives, that Eli Lilly gives, and as you can see, actually at the end of Bill's talk when he was saying what the Society of Nuclear Medicine is doing, as well as the American College of Radiology, we are in complete consensus with you that that is something that is highly recommended.
DR. MOCK: Great, I appreciate that, and I look forward to when it goes beyond should and it's an absolute requirement, for the reasons that we've mentioned.
The second issue is really part and parcel of that discussion, and that's around

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access. I understand and I appreciate all of you being here, and I understand that you're experts in the field, and it seems as though most of you are from metropolitan centers, even Fort Lauderdale I would think is a larger area. But we're talking about Medicare beneficiaries here, we're talking about the disabled, we're talking about the special needs plan members, talking about the elderly in rural Iowa. What about access when one of the use criteria is to have a memory expert evaluation? Has this been discussed, where is it in the plan? We've talked a lot about appropriate use. Will all of our Medicare beneficiaries have access to the scan today if number one is to have that appropriate specialist memory expert evaluation?
DR. SUBRAMANIAM: Would the CMS and the panel consider setting up a registry along the line of NOPR, whereby before getting your scan a clinician has to do all the workup, fill out a form, get a scan, and then after the scan the clinician has to fill out the end of the form to say how it's changed the management. That way you control the input, who gets the

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scan, and also the data collection. Would CMS be interested in a similar plan?

DR. FOSTER: As a member of the appropriate use committee we did discuss this a lot and we had a lot of issues concerned -- I'm sorry, Norman Foster, University of Utah -- and there were a lot of concerns raised about this specification. However, we believed as a committee that the expertise to appropriately integrate the information from an amyloid PET scan was critical and that there could be misuse, misinterpretation unless it was incorporated into the study or into clinical care and decision-making.

So for example, not every surgeon should be, would be expected to do open heart surgery, you have to have the expertise to be able to do that. I think that if this is covered by Medicare, then it's likely that there will be more impetus to develop the expertise to provide good care. It doesn't, I have to admit that it doesn't exist in large parts of the country. I serve patients in the intermountain west and currently we do not have clinical amyloid available because the

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radioisotope is short lived, and so again, it will make a difference whether this is reimbursed or not, whether these services are available.

DR. REDBERG: I have a follow-on to Dr. Mock's question about the expertise, because I noted in the Clark study which a few of you, I think Dr. Pearson and Dr. Mintun referred to, the FDA study for Amyvid, the readings that were done were done each by three different readers. What was published and I think what you summarized was that you averaged all those readers. But in actual practice that's not what actually happens, and what actually happens is one radiologist reads the study, and my understanding of the data from the literature reviews is that the sensitivity ranged from 55 to 90 percent for those three readers, and the higher number was from averaging those three. My radiology colleagues tell me that PET amyloid scans are among the hardest to read of all types of PET scans and therefore I'm just wondering, you know, if we take that 55 to 90 for individual readers, that's not great sensitivity for a diagnostic

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scan that has very serious implications for our Medicare beneficiaries.

DR. MINTUN: So, a couple things. This is Mark Mintun. The study you're

referring to is actually a study in which the readers were asked to rate the images on a scale of one to five, and that was usually the correlation numbers. Post hoc you can go back and say let's draw a cutoff here or there. Some readers had a different part of the ROC curve. That is why that study looked, it was not actually intended to look at diagnostic performance, it was supposed to look at the technical correlation of Amyvid uptake to number of plaques in the scan and the amount of amyloid on the brain.

The subsequent studies are the ones that looked at diagnostic performance and those are the ones, you're absolutely right, the first one looked at the diagnostic performance of the scan, which is a majority read looking at the understanding of whether the scan actually has the information you need to measure whether there was significant levels of amyloid, and that's the one that showed 92 to

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96 percent sensitivity and 100 percent specificity.

Then subsequently we have the third study that was discussed, and that is looking at whether we can train readers, that then look at two things, we can look at their reliability across the reads and we can look at their sensitivity and specificity on an individual reader basis. That study was not a majority read or consensus read or anything like that, that was individually. The numbers you quoted are not from that study. The study three, which is the third Phase III study in the package insert, in the FDA review, was carefully reviewed by the FDA. And that's the one that if you look at those scans, and those patients who died within a year of their scan, that's the one that shows the typical reader, the median reader is sitting there with sensitivity and specificity with in-person training in the 90s, and sensitivity of about 89 percent for the electronic trained.

Now, sure, there's a range of performance of doctors. These physicians had to do this training on their own, often in

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their office, stealing time away from other activities, they did this, then they did the reads. But this represented a range.

You mentioned that people consider this scan hard to read and I, certainly there are things that are hard to read, also compared

to other PET scans. I have been doing FDG scans since 1981, we have seen PET brain FDG scans for a long time in the field of radiology. This is brand new, this only got approved nine months ago. I do not expect people to say oh, I know this perfectly cold. I think it's reasonable to be, in fact I think I'm glad they say I'm going to take extra time to think about this.

So just to put it in context, that's the data that the FDA looked at and reviewed on this concept, and that's what I would like to focus on.

DR. ZEMAN: Dr. Mintun, can I just follow up on that, because you asked my question, Dr. Redberg. A number of the articles talked about the SUV relative to the cerebellum and some of the articles, the Clark article says that the qualitative read or the

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binary was equal to that of the SUV value, others said that the SUV value was actually more specific. What's your take on that, should we be looking at automated ways to get those SUV numbers, or is there some pitfalls associated with that, before this rolls out in the community?

DR. REDBERG: Thank you, Dr. Zeman.

DR. MINTUN: It's a good question and it's not the first time it's been asked. We obviously focused our clinical trials on the performance of the readers interpret the scans and that's what was being approved. The FDA also saw that same data as an exploratory analysis in a laboratory setting where these scans were analyzed blindly by software development at Avid Radiopharmaceuticals. That quantitation did very very well at predicting the pathology, so it's certainly something that's important to investigate.

Multiple vendors are investigating how to take such things as quantitative amyloid uptake in 25 amyloid scans and turn them into, you know, a useful number, but I think we have to emphasize that as we go forward, there may

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be advances in our knowledge of how to use amyloid scans such as quantitation, and how to integrate quantitation with the reads.

I don't think, there are very few parts of radiology where we're ready to say we're going to let a computer program read the scan and not a human look at it. I think this is going to be where we, I can see a situation

where we might evolve, with the right data collected, into a situation where this augments our read, but I see that as something that will only make, I would hope that this would not be adopted until we've shown it to actually improve individual reader's accuracy and reliability.

DR. REDBERG: Dr. Sedrakyan and then Dr. Rosenbaum.

DR. SEDRAKYAN: I wanted to comment about sticking to the evidence really, I think this is a really important issue here. Dr. Redberg alluded to a particular question and talked about a particular question, and I want to solicit your responses as experts in this field, and would them like them to be on target.

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A critical issue is that I think while we're not necessarily Alzheimer experts, we can draw parallels with other health care interventions and therapies provided in interventional medicine. I mean, surgeons are guilty of providing surgeries that have been shown to be very ineffective and harmful. Until 20 or 30 years ago we would do insufflation to grow coronary arteries, or tie many arteries to grow coronary arteries in ischemic heart disease, and all those surgeons were advocating for those services and practiced for a long time, and were very convinced that they were providing the best care that they can for the patients.

So I would like to ask Dr. Pearson to comment on the evidence about neutralization and use of therapies when they were negative and positive scans in the studies that he analyzed. I think you talked about a particular study when the negative scan still led to over 25 percent of patients receiving Alzheimer's medications, so clinicians did not necessarily change their management strategy in a substantial portion of patients but continued

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providing Alzheimer's medication, and that reflects an uncertainty on this end whether the test was valuable for them.

DR. REDBERG: And some doctors, it looks like, started Alzheimer's medication after the negative scan, which again, I mean, I think there's a clinical diagnosis in a scan, and maybe people are treating the patient, not the scan.

DR. PEARSON: This is Steve Pearson.

All of the information that I have is from a single study, which is the Grundman study, and it's all in one table, Table 5, so if you have access to that you can read along with me. But I would just preface, all of the numbers in here, and it is easy to forget, these are records of physicians' intended management, both before and after receiving PET amyloid results. So we can know what they said they would have done and what they said they would have done after seeing the test, but that's not the same as having a study that has hard data, if you will, on the action of clinicians following a test result.

So as Dr. Redberg pointed out, there

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are signs in this Table 5, and again if you break it down in different ways you could use all subjects, or those who were amyloid-negative and those who were amyloid-positive. I'm making some generalizations here but in both groups -- let's see, I'm sorry, in negative subjects, it said that 57, or 49 percent of patients had an Alzheimer's medication intended in the management plan before the scan, and 30 percent, sorry, 30, or 25 or 26 percent of all patients still had an Alzheimer's drug in the management plan after a negative scan comes back.

So I agree. I don't treat many Alzheimer's patients, and certainly I'm not the primary decision-maker over these medications usually, but I think there are reasons to ask why that would be and what it means. But again, I would just preface all of these numbers that do show some changes in the treatment regimen, that these are intended results and not data on actual outcomes.

DR. SEDRAKYAN: Any final comments on this same topic?

DR. MINTUN: I'm just throwing, I

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guess in two ways, one is that that study, you know, is the glass half empty or half full? Here is a test which gave them information, and they reduced by half the amount of use of Alzheimer's disease medications. So you can say it didn't go to zero, and of course individual patients and individual physicians have to make that decision, but it did reduce it by half. And so, you know, I think it's an important consideration to sort of look at the whole study.

You know, one of the other things that

I think we have to do, you're in charge with the question in front of you, what is the data related to benefits to the patient in outcome, and I think what you're hearing is that there is no one study that takes amyloid imaging, randomizes it where we have, you know, standardized treatments, follow the patients. Alzheimer's patients are complicated, it's difficult to measure their quality of life, their cognitive performance at any given time, so you have to do that over a long time or do it many many times and going all the way out, until we can demonstrate it. And as a study of

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a process that has just been approved, I think it's clear there is no study that does that for amyloid imaging from beginning to end. And so the question would be, is there any other evidence, and what we're trying to point out is that there is evidence related to outcomes. Is it a single study that goes from beginning to end, no. Is there studies demonstrating that there is clinical utility of getting a better diagnosis, potentially an earlier diagnosis, a more correct diagnosis, ruling out misdiagnosis, yes. Are there treatments approved by the FDA that admittedly are not as good as we would love them to be but have been approved by the FDA because they have shown benefits to the patients, they've shown outcomes, yes. Have there been studies showing that once someone gets a diagnosis, there's better management of their comorbidities after the diagnosis of Alzheimer's, yes. So the question is, you know, is it easy to put that together? I think that's why you've been called here. It isn't black and white, how to put that all together. What we're saying is that, and what you're hearing a

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little bit is the frustration that this data exists out there in the field and is being used, but hasn't been assembled all in one place. And so one of the things that, you know, I think, as I concluded, with the totality of the evidence and the individual pieces that have to be linked.

DR. REDBERG: Right. I mean, I think it's clear that there are FDA-approved drugs for Alzheimer's that help modestly some minority of patients for at least a year, but it's not clear from these data that have been presented as to what the role of amyloid scan is in those studies because it hasn't been

studied.
SPEAKER: Well, to answer specifically on the Grundman question, I was involved in that study, and for example, if you're seeing a patient and vascular dementia might be in your differential diagnosis, the scan comes back negative. Even though cholinesterase inhibitors aren't typically approved for that, most of us are using it. If Parkinson's disease dementia is in your differential diagnosis, some patients will have positive

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scans, but many will not, and then you will still be using a cholinesterase inhibitor even though the scan was negative, so I think there is a good explanation.
DR. SEDRAKYAN: I want to follow up on that because this is really an important issue in resource usage. You made a very strong statement, the panel made a strong statement about the value of negative testing in ruling out, or increasing your confidence that these patients will have Alzheimer's. That also acknowledges that a substantial portion of your practice is inappropriate right now. So I wanted you to comment on that. Can you put a figure around that, is five percent of your practice inappropriate, 20 percent, half of it? And which subpopulations can we identify where your practice is more likely to be inappropriate, can you say which subgroup of patients that more likely will get it wrong and really these tests will help to eliminate those patients who are being treated inappropriately? Because this cannot be applied on every patient, you need to say where am I more likely to be wrong, and I'm treating blindly.

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SPEAKER: Well, we know that 20 percent of patients who are diagnosed with Alzheimer's disease will have negative evidence of Alzheimer's pathology postmortem, so the number is about 20 percent. When we did the clinical trials -- now we're not recommending we study the typical patient that we think has Alzheimer's disease, that's not part of the appropriate use criteria, but it came up in the clinical trials, and I think what you end up doing is scratching your head and saying okay, we're not dealing with Alzheimer's disease, does this patient have frontotemporal dementia, or should we be looking more carefully for depression, or is there vascular dementia. There's something else going on and it makes

you rethink the clinical situation and often change medication and come to a new diagnosis.
DR. AISEN: I think there's a variation in practice and unfortunately that's leading to increased confusion, but I want to make a few points. One is that what an Amyvid or amyloid PET scan tells you, in my opinion, is, whether you have Alzheimer's disease or not, that the 30 percent of normals with a

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positive scan --
DR. REDBERG: You said earlier that it tells you whether you have amyloid, not whether or not you have Alzheimer's disease. Are you changing that now?
DR. AISEN: The indication is for amyloid. I said what I believe, because amyloid -- you asked this question before. No, amyloid causes Alzheimer's disease, the evidence is extremely compelling, amyloid causes Alzheimer's disease. The presence of amyloid in brain, I believe, and I would say there is only 80 percent consensus on that, the presence of amyloid in brain means you have Alzheimer's disease. What it doesn't tell you is what stage you're at, asymptomatic or preclinical, MCI or prodromal, or dementia AD. Therefore, an amyloid scan doesn't tell you whether you need treatment. Treatment only works in people with AD dementia, and treatment that is drug therapy is a very small part of therapy. I don't actually believe that amyloid scanning is helpful in deciding who should get drugs today for Alzheimer's disease, because the drugs are not very dangerous, they can be

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tried. Most people benefit. It's a misconception that only 30 to 40 percent benefit, and it's a misconception that the benefit is only one year. It is a modest benefit, impossible to look at in terms of responders, because we have no measures that can do that. But every study has shown consistent group-wide findings of benefit and they go on for as long as you continue treatment. But there is not much of a price to pay for treating amyloid-negatives because these aren't very dangerous drugs.
The advantage and the price to pay of not having an amyloid scan is not being able to tell people whether they have Alzheimer's disease, and that has extreme prognostic value in the prodromal MCI stage, and many studies have proven, there is no question about this,

you can tell that someone has a 50 percent likelihood of being functionally severely impaired in two to three years because they have a positive scan, versus a ten percent or less likelihood if they have a negative scan, and that is hugely valuable for planning, for safety issues, for counseling, for long-term

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care planning, and that's the value of the imaging. It's hugely valuable, not for deciding who should be on drugs today, but for the other aspects of AD care.

DR. REDBERG: I have Dr. Rosenbaum.

DR. ROSENBAUM: I think there's some corollary in Murphy's Law that if you wait long enough, your questions before become irrelevant, but that won't stopped me.

So, I was going to make one comment about the issue of the Alzheimer's drugs, which I don't think is an important issue because they shouldn't even be called Alzheimer's drugs, they have a particular mechanism that's called cholinesterase inhibitors that are used for a variety of things, and all doctors use things off label, and in my field we use them for memory problems that may not be related to Alzheimer's or other cognitive problems, so if people choose to treat somebody, that's just because there are no really good drugs to enhance memory. So I don't know if we can look at that as change one way or another as a benefit.

The other comment I was going to make,

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and the recent discussion may have borne on that, is I had a sort of sense that we're getting into indication risk, and so I came here thinking we were looking at a test that would tell you that you weren't likely to have Alzheimer's, or you did have Alzheimer's, and it seems like a lot of the discussion was that we were making a diagnosis, it was definitive and so forth, and I appreciate that that's what the clinicians believe, and that what's constrained in the indication may be something different. But I just wanted to point that out, that there was this sense of drift that we're using this to make a positive diagnosis, and at least some of you said that.

So I would like some, I guess to hear some comment on that, because that drift speaks to a larger and more important issue. For example, last night when I got to the airport and grabbed today's Globe, nothing more to read

about in Boston sports, so I turned to the front section and on the second page -- and this is my first time on this committee -- so I was struck by the release of this seminal article on the eve of the meeting and the -- I

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pick up a newspaper and there's an AP release, and it says advanced imaging that detects plaque in the brain should be covered by Medicare and private insurers for select people with dementia to help diagnose or rule out Alzheimer's disease according to guidelines released Monday.

And so, if there is this drift that we have a test to diagnose Alzheimer's and if we're talking about it here, I just wanted to get a feeling from the committee whether, you know, this drift that is occurring and it's going to happen in the media, happened a little bit in your discussion, is it a good thing or a bad thing, and, you know, and what do you really feel about that? Are we really going to rein it back a little and say this is just going to tell us that it's not likely to be Alzheimer's, we've got to look somewhere else, or are we hedging a bit?

And then after that's discussed, I do have one other issue that I would like to bring up that has more to do with the appearance of, you know, conflict issues that I just want to raise, not because I'm biased one way or the

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other, but I just want it to come out in the open, so if I could come back to that question after people comment on that last comment.

DR. REDBERG: Okay. Anyone want to comment on that?

DR. FOSTER: Norman Foster. And so, I do not believe that amyloid PET imaging is a diagnostic test for Alzheimer's disease. Only physicians can make a diagnosis of Alzheimer's disease. Imaging does not diagnose disease.

And so as I've said on several occasions, this is one piece of information that has to be used by the physician, a very important piece of information I'm arguing, to determine a diagnosis. And I think that all too much has been placed upon -- it's important what the technical performance of the test is, but how it is used in clinical decision-making is really the issue, so I hope that answers it.

It's not a diagnostic test for Alzheimer's disease, it tells us what the pathology is, it's a piece of information.

DR. SALLOWAY: This is Steve Salloway. The amyloid PET is a major advance, I think, in the diagnosis of cognitive disorders, because

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it detects the molecular pathology, or either the presence of or lack of the molecular pathology of amyloid in the brain, and it does so consistently as has been consistently shown now with a number of tracers, not just one tracer, with high sensitivity and specificity. Where I think it has the greatest -- and I think the package insert says that it's used for the detection of amyloid pathology which is consistent with Alzheimer's disease, or the lack of, which suggests that Alzheimer's is less likely. And I agree with what Norm just said. Where I think the test has the greatest utility, and I really agree with the appropriate use guidelines, is there are patients who come in, especially in the MCI stage, and MCI is not a diagnosis, it detects the level of impairment, it doesn't say what the disease is, it says the person has mild cognitive impairment. And there are many of those cases where it's unexplained what the etiology is, some of them will be due to Alzheimer's disease and some will not. There's a very high likelihood, as you heard Mark say, that people who have MCI and

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turn out to be amyloid-positive will progress to dementia. If you follow them long enough, almost all of them will, some faster, some slower. Those that are amyloid-negative, a very small percentage will. So you can tell your patient now that it's only one piece of information that you're integrating into the evaluation and that's why a dementia expert should be involved with this, it shouldn't be approved for routine use, there needs to be guidelines to focus the use.

But you can tell the patient that you, and one of the cases I discussed had MCI with a very positive amyloid scan, a positive family history, a number of factors that went along with the diagnosis, and I said with fairly high confidence that she had MCI due to Alzheimer's and I was very concerned about her progression, and that directed the care and the kind of support services that she needed. And conversely, if it were negative, I would have counseled her much differently, and also opened up other options for treatment as well. But this is where I think the greatest utility that

this test is going to come in is in those cases
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with MCI or the diagnostic uncertainty.
DR. REDBERG: Thank you, Dr. Salloway.
Dr. Rosenbaum, you had a comment, and then I have Dr. Herscovitch.
DR. ROSENBAUM: Just to have some discussion on the issue of conflict of interests and to be clear, I don't think anybody's expertise degrades the degree of interaction with our colleagues in industry, that's not the point, but just with something as important as this, I just think we should all have as clear awareness of relationships as possible. And starting, you know, with this experience of getting on the plane and reading what I was supposed to do the next day and, you know, the timing of the release, so we know this is an important issue that people care about, and they're going to go to all efforts to get the decision they believe in.
But I also wanted to ask in particular, given the importance of the appropriate use document, really just a couple of questions. One is that the societies that collaborated in sponsoring this document, it's not clear from the reading of it to what extent
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their activities with whatever travel and writing and meetings were sponsored, and I think to the extent there was funding for that through the societies directly for this purpose, it just should be known about. It appears that the vetting of conflict was outsourced to an outside agency rather than the society itself, so that struck me as a little unusual and I would like to understand that better, and how independent their funding was from the manufacturer.
And finally, it does say that the societies rigorously attempted to avoid any actual, perceived or potential conflicts, and then had a bar of 12 months and greater than 5,000, but it doesn't tell us whether in the previous years people made, you know, gazillions. And then when you go to the table of relationships, almost all of the authors in fact have reported relationships with either the original or current owners of the compound. So not wanting those kinds of observations to emerge, you know, elsewhere or down the road, I thought this would be a good time for people to clarify those questions for the committee.
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SPEAKER: Let me try and address the issue of support first. The project itself was entirely supported by the two organizations with no funding from any outside group, and in terms of conflict of interest, I'm not quite sure what your reference is to conflict of interest coming through an outside organization. I think both agencies were particularly careful about conflict of interest here, primarily because we recognized that there are going to be significant issues around income to certain companies. And so there was a lot of discussion within the group itself about what was appropriate and I think we used what were essentially modern standards. The fact is in putting together a document like this, if you eliminated anyone who had any conflict, you would be hard pressed to put the document together. So in fact one of the people who actually knows the most about this particular topic is Dr. Phil Klunk, who as you know, with Dr. Chet Mathis, really developed Pittsburgh compound B, and while he was an advisor to this group, he's not on the authorship group and he was not a voting

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member, because it was regarded as he had too much of a conflict with the process. So I believe both organizations are really using what I would think of as modern conflict of interest rules and we would be happy to get you any further details about that, if you would like.

DR. REDBERG: Thank you for the comments. I assume, Dr. Rosenbaum, you were talking about Table D-1 in the article, which has table of relationships with industry and other entities, and listed the other reviewers, which noted that 10 out of 14 had listed relationships, many of them multiple with industry.

But I do want to note, we are getting close to the time for voting and there are several panelists who haven't had an opportunity to ask any questions, so I have listed Dr. Herscovitch and then Dr. Sanders.

DR. HERSCOVITCH: Thank you very much. First, I just read the ICER report which says that among things insurers will be looking for was contextual considerations, precedent set by prior coverage determinations for similar

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technologies and conditions. And then looking at the CMS approval for FDG, quoting from it,

it says: CMS considers the evidence adequate to conclude that FDG-PET improves net health outcomes by assisting in the detection of frontotemporal dementia, and so forth. And in many ways the overall discussion in that decision was similar to some of the things that we've discussed today, expert evaluation, uncertainty in the differential diagnosis, qualified readers, and of course a discussion of outcomes.

So I guess my question is, how should that prior determination by CMS inform any future work that might have to be done either to lead to CMS approval or how CMS might ultimately view this particular application, given that prior decision and that ICER statement?

DR. REDBERG: Dr. Herscovitch, I think, I mean, I worked in the Senate at the time of that decision, and I think there were a lot of intervening factors using the technology assessment which was not favorable for FDG-PET, and the political decision which had some other

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intervening factors that were described in the Washington Post article and others, so I'm not sure that is totally relevant, and I think we already discussed the FDG-PET. Unless you think it's relevant to our voting questions, I'm going to try to stick to the discussions that will help us inform the voting questions, and we can come back to that one afterwards.

DR. HERSCOVITCH: I'll pass.

DR. REDBERG: Dr. Sanders.

DR. SANDERS: Amy Sanders. My question also pertains to outcomes, because this morning when Dr. Frank spoke to us, he raised the possibility that the outcomes, which is the standard against which I guess we're supposed to judge this, might be inappropriate because this is a diagnostic test. And I'm concerned because I find that outcomes are an undefined variable, so I'm somewhat insecure about how to proceed given that I don't have the ability to define the standard against which I'm supposed to make a judgment. Outcomes were defined at another point in the day as overall survival and progression-free survival, and I understand that those might be

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appropriate if what we're talking about is cancer, but that's not what we're talking about.

So I would like to invite, if I could,

the experts to offer some comment on how they understand outcomes to be defined for our questions, and if they include patient-reported or patient-centered outcomes.

DR. SUBRAMANIAM: Rathan Subramaniam from Johns Hopkins and the American College of Radiology. The outcome for this can be best defined in two paradigms. The first paradigm is change of management. The second paradigm is quality of life. Because mortality in this case, there's a huge time interrupting the test and mortality.

So if I take it to the end of the paradigm, CMS has accepted change of management as a patient-weighted outcome already in its determination for FDG-PET for oncology. Hence, I think change of management should be considered in this case. That's one.

I say health policy experts, I think it also relates in this case how a patient functions, so a functional outcome before and

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after the test, how it changes is probably valuable, because you can hear from our clinical colleagues how they make the decision, change the treatment or not change the treatment, and how patients make decisions, so I think those are things very relevant to this question.

DR. REDBERG: I would consider an improvement in outcomes, outcomes have to be something that a patient can appreciate. So if the change in management was clearly linked to an improvement in outcome or, on the other hand, a detriment in outcome, that would be a significant change in outcome, but it has to, outcomes are something that patients can feel, and feel the improvement or feel the detriment.

DR. SANDERS: And would you extend that to caregivers in that definition under these circumstances, given the patient population we're talking about?

DR. REDBERG: I don't know if Louis wants to comment, or anyone else from CMS. I think that a patient unit includes their family.

DR. FRANK: Richard Frank,

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representing MITA. The case we're making is that diagnostics are different. The intent of the diagnostic intervention is to resolve a diagnostic dilemma, to stage patients, to lead to a treatment choice, a better informed treatment choice. And therefore, the outcome

of a diagnostic intervention is that differential diagnosis or that staging contributing to a therapeutic decision. So we're not saying that we shouldn't follow the diagnostic to an outcome, we're saying that the outcome of the diagnostic intervention is different than the outcome of a therapeutic intervention.

The outcome is the decision to treat and the choice of therapy. It shouldn't be necessary for the diagnostic trial to prove what we already know, which is that if you choose the wrong therapy because you've not diagnosed disease correctly, the patient is not going to get better.

This is part of the basis for the approval for FDG distinguishing between frontotemporal dementia and Alzheimer's, because the treatments for fixed disease don't

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work in Alzheimer's and vice versa. So if you can simply show that detecting a pattern of glucose utilization will distinguish between FTD and Alzheimer's and therefore choose the appropriate therapy, you shouldn't have to go on and run the trial to show that having chosen the right therapy you get an outcome, that's already known from the proof of the treatments, and in fact it would be literally infeasible if you were to require this of diagnostics.

So this gives me the opportunity to go back and ask the last question at the end of the first session today, which is would you be holding amyloid imaging to a higher standard, and the answer is yes, you would be holding amyloid imaging to a higher standard if you were to require cost effectiveness or therapeutic outcomes.

DR. REDBERG: Thank you very much.

DR. JACQUES: Just to clarify for people, current Medicare coverage for FDG-PET in this particular context goes in two different directions, one is essentially coverage with evidence development, and the other, which people have alluded to, is in

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certain patients who fulfill a number of criteria, the last time I looked at it the list was something like that long, that FDG-PET would be covered in that context. But just to remind everybody, there are actually two different coverage issues surrounding FDG here, it's not a monolithic policy.

DR. REDBERG: And I'm just going to

make a comment and then turn it to Dr. Fendrick who has another question, and then we're going to get to the votes.

My concern is still in the evidence that we've seen. You know, I think we have clearly heard that having amyloid does not mean you have Alzheimer's. There are people that die very happily with normal cognitive function and have Alzheimer's at autopsy. Telling someone premorbid that they have amyloid plaque, and I know you just said you believe they will get Alzheimer's, but what's not clear to me is what is the impact on our patients of telling someone that they have a 70 percent chance or whatever it is, because we don't know, of getting a disease that we all are terrified of getting because it's a very,

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clearly, there's going to be at least, I would say 30 percent, who are never going to have that terrible thing happen, but they will have gone through the trauma, the labeling and everything else associated with it. Do we have data related to that and how are we going to avoid having this happen with our Medicare population.

DR. SALLOWAY: This is Stephen Salloway. I'm so glad you brought that up, because I think there's been some confusion here today. According to the appropriate use guidelines, those patients who are preclinical, who are suspected of having preclinical Alzheimer's disease would not be included under the coverage plan because they are asymptomatic, they don't have the requisite cognitive decline. So there's an important area of research just to address the questions you asked, what's the impact, what is the rate of progression. That would not be included in the recommendations for coverage for CMS. It's for patients who have cognitive impairment where the diagnosis is uncertain and there's a high level of amyloid, that makes Alzheimer's

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quite likely in that person.

DR. REDBERG: And what would I do differently then?

DR. SALLOWAY: Well, as I said earlier, for patients if they had MCI, for example, and they had a positive amyloid scan as part of their workup, you would say the MCI is likely due to Alzheimer's, and you would mobilize the family to start preparing that person immediately.

DR. REDBERG: Based on their scan but not on their clinical presentation.
DR. SALLOWAY: No, based on the whole clinical evaluation including the scan, because we know that having a positive amyloid scan and MCI is a high rate of progression. If the scan is negative, the rate of progression is quite low, so you wouldn't mobilize all those resources, you wouldn't counsel them the same way. And also, there may be medications or medication trials that are available to them with the positive scan that wouldn't be available.
So, I know -- but the other point of your question is extremely important, something

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that I deal with every day. You really order tests for one patient at a time, you always want to assess what the impact of that test might be for that patient, and how finding out that they have an amyloid positive scan and a higher risk of Alzheimer's, what impact would that have on them. And that, we wouldn't routinely order that. We'd take the patient into account on what the impact on the patient might be.
DR. REDBERG: Thank you.
Dr. Fendrick.
DR. FENDRICK: I'm going to just make three points and then ask Dr. Pearson and Dr. Aisen some softball questions before going into deliberation, I hope relevant to the others.
One of the most interesting slides for us was that we were facing three important areas where a diagnostic test in the absence of a therapy might be valuable. One is the reduction of unnecessary medication use, which we kind of faced and thought that was not that big a deal, and I think the evidence would back it up. The second is delayed diagnosis of

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treatable conditions which, there's no evidence for that either.
So the third is this value of knowing which, value of information, that's something I have been studying for 20 years, and I don't want your comments, let's just say that it's huge, which I believe is the total response, is not consistent with the studies in the behavioral psychology that show there is a clear down side to this information in a whole bunch of people. And I strongly recommend that you come back for the world and the peer

reviewed literature to show that your huge is actually huge, as opposed to huge in some and really really bad, as we heard in the New York Times article.

The softball is about the gold standard, autopsy. Is it a 24-karat gold standard or a 12-karat gold standard? Because I would imagine at San Diego the pathologists are superb, they know what to look for, but I'm worried when you guys talk about false positive, false negative rates off the gold standard, that there may be issues there, variabilities.

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Steve, the question to you as we embark is just your best guess on negative and positive predictive values, since we've talked only sensitivity and specificity, and it may be only a best guess, but it will be very helpful for us as we move forward.

DR. BATEMAN: First, I just want to make very clear that I did not recommend clinical use of amyloid PET scanning in cognitively normal, clinically normal people, so if I've left some of you with a misconception, in no way do I recommend that, it's not part of the guidelines, it's not something I would ever do myself outside of a research setting. We're talking about amyloid scanning in people with cognitive symptoms.

And by the way, there was an earlier question on what that means, doesn't the entire aging population have cognitive symptoms? Yes, loosely defined, the majority do.

We have very precise diagnostic criteria for the symptom of mild cognitive impairment based on cut scores on episodic memory, so we know how to separate the syndrome of MCI from normal cognitive aging and the

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associated subjective complaints.

DR. REDBERG: Thank you. Dr. Bateman.

DR. BATEMAN: Oh, I can't finish answering his question? There is some fuzziness there, but the reason it's so important, the value of accurate diagnosis is so important in mild cognitive impairment is, the evidence in the literature is absolutely clear, it's the difference between a hundred percent certainty over time of progression to dementia and death, 50 percent over a two-to-three-year period, versus a 10 percent risk. And when you're talking to a patient and family, that's huge, and it's a safety issue

and a planning issue.
SPEAKER: Let me just clarify those numbers. I read somewhere here that at 18 months, 29 percent with a positive scan would have progression, 10 percent if you have a negative scan. Is that just a time thing?
DR. BATEMAN: Yeah, so I said 50 percent in two to three years, which is consistent with 29 percent in 18 months, and 10 percent in the negatives, right.
DR. REDBERG: I didn't see the longer

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follow-up data. Steve, in your review of the literature, did you want to comment past 18 months?
DR. PEARSON: Steve Pearson. No, I'm not familiar with any longitudinal follow-up beyond 18 months, that was the best study I could find. If there is other published data beyond that, it may or may not be as influential. Certainly Doraiswamy is the paper that most people talk about.
So I'll quickly take your first point and then take a swing at the softball. So, there are data -- in our group and white paper, we reviewed the psychological outcomes. There are no studies of psychological outcomes in patients undergoing PET amyloid testing. The closest analogy we could find was a relatively large study of patients whose genetic predisposition to Alzheimer's was revealed to them, it was the ApoE REVEAL study. And for patients who had a positive test result, that is they had a higher likelihood of getting Alzheimer's, they had increased stress for six months, after which it declined, and by about a year they were in the same ballpark as

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everybody else. The participants who had a positive status did report changes in prevention activities for Alzheimer's disease, changes in exercise, diet, what have you, and a higher rate of thinking about making changes to things like long-term care insurance. But again, no direct data from the PET amyloid community, this was the closest I'm aware of.
As far as the softball, actually I do remember doing a back of the envelope negative and positive predictive value, but the point that you raise is a very important epidemiological one. Any time you look at sensitivities and specificities, they are intricately linked with the prevalence or the prior probability of disease of the patient

population being tested. So that means that the higher the likelihood of Alzheimer's disease in the population, the higher risk of false negative tests, the lower risk of false positive tests. If you have a population with a relatively low risk of Alzheimer's disease, you will have a much higher rate of false positives and a lower rate of false negatives. So the only data we do have are from

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the relatively small studies that were used for the FDA approval, and I think it's important again to look at not just the sensitivity and specificity, but the rates of false positives and false negatives in that population, and the best you can, you can project that forward into a national scale and then think about the impact.

DR. REDBERG: What would you say is the prevalence in the small study that was done for FDA approval as compared to what we might expect in clinical use?

DR. PEARSON: That's a big hypothetical question. As a primary care physician my view, I think, would be very different than some of the specialists here. I anticipate nearly every single patient over the age of 50 would expect to get this test, like a colonoscopy.

DR. REDBERG: In the FDA study by Clark --

DR. PEARSON: I'm a primary care doctor, some of you are too, and that's my anticipation, if it were approved for coverage. I think the intense interest in this as

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demonstrated by media and others -- now, can it be managed appropriately through appropriateness criteria, through coverage criteria, I do think that there will be a tremendous interest. And I'm not saying it's not well deserved, I'm saying that I think there will be a lot of requests and that the overall population will include many patients with the earliest, if any, signs of MCI.

DR. REDBERG: Because my reading of this FDA study by Clark that was the three-multicenter trial, the small study that was done, was an end of life study for people that died within a year, so that clearly, I would expect that the prevalence would be higher and so the sensitivity might be higher because the prevalence was higher.

DR. PEARSON: Again, Dr. Mintun could

tell you more if he gets a chance, but that population, it was obviously distinctive, these were patients who were considered to be near the end of life, but there was a relatively high percentage who were cognitively normal, it did not have to be patients who were dying of Alzheimer's disease or dementia, so how

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representative it is of those patients who would seek out testing or be recommended for testing, I think is definitely a judgment call.

DR. REDBERG: And then the other part of that study in the specificity cohort to evaluate false positives, that was done in young subjects who were negative ApoE4, and again, a young population where you would expect prevalence to be low, and specificity would not be presumably as good in an older Medicare population.

DR. PEARSON. Right. And I think this is probably part of the reason why the FDA in its postmarketing requirement asked the company to continue doing studies comparing the inter-rater reliability of the findings, because it will be used in different populations going forward and I think there's going to be continuing interest in how reliable and high the inter-rater reliability is with these tests.

DR. MINTUN: There was a very large study that indicated -- well, I mean, I'm going to have to say that gingerly with this group. The A17 study was 229 people, the concept was

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that this is very similar to the population, it's certainly very similar to the population on label, which is patients who have cognitive decline so they're not screen normal, those people are rejected, and I think should be rejected, but cognitive decline and suspicion of Alzheimer's disease. The person was not allowed to just come in and say I'm cognitively declining, I think I know what it is, but let's do this scan anyway, they had to have a suspicion of Alzheimer's disease, and yet not certainty.

If you look at the appropriate use criteria, independently they came up with the same concept. How do we identify those people in which the diagnostic dilemma is important, and what did we see? If you look at A17, the number of scans that were positive and negative were about 50-50, which means they were actually very good at coming up with those

scans, those subjects that did have a diagnostic dilemma. So I just want to point out, that actually puts you in the sweet spot as far as NPV, negative and positive predictive value, but I just want to point out, that is

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the best data we have for how this would be used in the regular world.

DR. REDBERG: Just to reference the postmarketing surveillance, have those studies started and are there data available from that?

DR. MINTUN: It's not postmarketing surveillance, it's a postmarketing commitment, of which the concept was that we offered to the FDA that we would investigate quantitative processing of images to evaluate whether this could be used as an adjunctive visual read, and we offered to the FDA and was accepted, a postmarketing commitment to evaluate physicians reading in the field, so that we would have an idea of which training methods seemed to be working in the field, in other words, not in a clinical setting here. So this is to evaluate how those training methods are working, those protocols are being reviewed by the FDA, and we will be going back and forth in developing this protocol.

DR. REDBERG: But you're not formally tracking patients who have gotten the scans?

DR. MINTUN: We're not formally tracking any reads, we're not doing any

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surveillance of that.

DR. REDBERG: Thank you very much.

Dr. Mock.

DR. MOCK: Curtis Mock. Clarifying a question, I had jotted down something I thought you had said, and in the interest of voting, I wonder if you could clarify. Since we're confined to evidence, I thought I heard you say that the study showed that once a member or a beneficiary or a patient is diagnosed with Alzheimer's, then there's, the study showed that there's better care of their comorbidities. Which study was that, and was that included, I wonder, in our literature?

DR. MINTUN: I would like to ask Bill, who explained that study to me.

DR. THIES: I think we actually don't have it in the literature because we didn't anticipate the need, but if you look at the Journal of American Gerontology, a 2012 article, the lead author is J.R. McCartin, it shows that in the VA system where people were

identified as having dementia with a screening program, that they in fact had better care and reduced costs.

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DR. MOCK: In the VA system?
DR. THIES: Yes.
DR. MOCK: So there's evidence there that we didn't have to evaluate for this discussion that showed that?
DR. THIES: Yes.
DR. REDBERG: I haven't seen that data. If you have an extremely brief comment.
DR. SALLOWAY: In answer to the longitudinal follow-up, there's a very good correlation between CSF, A-beta and tau in amyloid PET. The ten-year data with CSF, those were MCI and a positive amyloid and tau, progressed to Alzheimer's disease about 95 percent over ten years, and it's about 15 percent in the amyloid negative group.
DR. REDBERG: Well, the April 2011 NINDS criteria, they do not advocate the use of AD biomarker tests for reaching diagnostic purposes at the present time. More research needs to be done to ensure the criteria that could be used are appropriately designed with standardization.
DR. SALLOWAY: Just to your point, this paper came out in 2012, since then, and

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this is the latest data we have about predictive benefit.
DR. REDBERG: Okay. Thank you. I want to thank all of the speakers for a really excellent job. We appreciate all of the effort that all of you made to bringing your expertise and the data to bear on the panel.
At this time I will call the first voting question, which I will read, everybody has their clickers. How confident are you that there is adequate evidence to determine whether or not PET imaging of brain beta amyloid changes health outcomes (improved, equivalent or worsened) in patients who display early symptoms or signs of cognitive dysfunction?
One is low confidence and five is high confidence, you can vote anywhere from one to five.
MS. ELLIS: What we're going to do is for the panel members, the voting panel members, you have your key pad. All you have to do is hit the button one through five, you can hit it as many times as you like, but your last vote will take. And then what we'll do

is, also, you do have an orange sheet in your
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folder, so please also record your score on that, because I will collect it at the end of the meeting.
After everyone has voted, we will go down the row. If you could state your name and your vote, it will be greatly appreciated.
Please keep in mind, we need you to speak directly into the mic, because we have our transcriptionist who is in another room, and we have individuals viewing the meeting live, so that they can hear you also. Thank you.
(The panel voted and votes were recorded by staff.)
DR. JACQUES: While we're waiting on two people, this is Louis Jacques. I just want to remind everybody in the room that the MedCAC recommendation is a recommendation about the evidence, the MedCAC does not make coverage recommendations and the MedCAC does not determine coverage. Those are essentially the authorities of the Secretary, which we exercise on her behalf. If there are people who believe that there are studies that may be published after this particular meeting or other things that were not considered, you are certainly
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free to bring them to our attention through the coverage process.
DR. REDBERG: Okay. So we have, the scores are in, the mean was 2.167, with three members voting low confidence, five members voting a two, so between low and intermediate confidence, three members voting intermediate confidence, and one, member voting between intermediate and high confidence, zero members voting high confidence. Okay. So we're going to go down now and discuss our votes.
DR. SEDRAKYAN: Art Sedrakyan, two.
DR. REDBERG: Okay. We'll go down first and just say our votes, and then we can discuss it.
DR. COZZENS: I wanted to vote 2.5, but I voted three.
DR. FAUGHT: This is Ed Faught, I voted three.
DR. FENDRICK: Fendrick, two.
DR. GUTMAN: Steve Gutman, I voted one.
DR. HARTMAN-STEIN: Paula Hartman-Stein, I voted one.
DR. LEVINE: Susan Levine, I voted
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one.
DR. MISKIMEN: Theresa Miskimen, I voted two.
DR. MOCK: Curtis Mock, two.
DR. ROSENBAUM: Jerry Rosenbaum, two.
DR. SANDERS: Amy Sanders, four.
DR. ZEMAN: Bob Zeman, three.
DR. SEAL: Brian Seal, three.
DR. HERSCOVITCH: Peter Herscovitch, four.
DR. LYKETSOS: Constantine Lyketsos, three.
DR. REDBERG: Thank you. And now we can have some discussion.
DR. JACQUES: And just to remind everyone, the votes that go up are the votes of the voting members, so although some of the guests may have had other votes, they are guests, so the calculations are done, and the display is the votes of the voting members.
DR. REDBERG: And the chair doesn't vote.
DR. SEDRAKYAN: I think the main evidence that led me to vote two in this instance is really uncertainty that I have in

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terms of the value of reducing this inappropriate therapy and how much harm is associated with that, and also uncertainty related to false positives that certainly can occur, and how much the harm associated with false positives can outweigh the benefits associated with reduction of this inappropriate use and also knowledge, knowing. So I'm not sure I have enough data to be able to make that, weigh the benefits and harms of this particular technology in terms of the false positive aspects and potential for reducing uncertainty for the patients related to whether they have Alzheimer's.
So again, the medication management, I think I would have voted three if I would be able to come up with a subgroup where I would see that inappropriate use is really high, and I didn't hear from the panel that we can really come up with that specific subgroup of people that were more likely to be wrong, it's really everyone, and we can't narrow down to some subgroup where we can see this inappropriate use and potentially have the beneficial balance of knowing versus false positive. I think I

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would have voted three.
DR. COZZENS: Jeff Cozzens. I think

that there's too few studies that -- I applaud the fact that this has only been around for a few years and there have been a great number of studies that have been done in those few years on this issue, and I think that that's very important and I think we need to see more studies. I've taken a lot on faith, but I think as far as the actual number of studies and the questions about is there adequate evidence, I think that there's some evidence for each of these issues but not enough to say that it's a four or five. Like I said, I really would have voted 2.5 on this, but I think that fate has put me up to three, and I think that I want to see more studies, I really do.

DR. FAUGHT: Ed Faught, I voted three. As a neurologist, I think this would change the way that we manage patients and I would like to have it available from that point of view. On the other hand, I see a big potential for overuse and misuse if everyone has this like a colonoscopy, so I found it a little vague. I

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applaud the criteria, they're good criteria, I'm just not sure how they're going to be enforced, and how are we going to make sure that people who are dementia experts really order these tests.

DR. GUTMAN: Well, I take exception to the notion that the outcome can be just a change in the test behavior or in the diagnostic behavior, I think treatment does count. But my real problem here is that I think on the Fryback-Thornbury scheme it doesn't pass level two, it actually doesn't have diagnostic accuracy or clinical validity established. I don't believe you can take the pilot studies that FDA looked at or other studies from the literature in which there were highly enriched populations of Alzheimer's disease positive and cognition normal patients and in any way translate them into something that's relevant to the model that you're proposing. I think the model that you're proposing is actually good and reasonable, I just can't connect the dots between what the current state of knowledge is about the way the test performs and the outcomes. I don't think

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you can create a chain of evidence here that works.

DR. HARTMAN-STEIN: Paula Hartman-Stein. I think there's not enough

research yet at all that looks at quality of life outcomes. Simply whether or not the physician is giving medication or not to me is inadequate in terms of looking at the value of this test.

DR. LEVINE: Susan Levine. I agree with what's been said about the inadequate evidence base, both related to the change in patient outcome or patient management, or in patient-centered outcomes. And I also feel that the studies that are needed can be done. I know there was a comment made about how Alzheimer's disease patients can be hard to study, but it was my understanding from listening to the discussion today that the value of this imaging is primarily in patients for whom there is some question, so those who are not severely affected at least as yet, and so it seems to me that it is perfectly reasonable to expect studies be done in those populations.

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DR. MISKIMEN: Theresa Miskimen. I concur with what I've been hearing, and specifically about the fact that more studies are needed. I could not connect the dots, I was really trying to connect the dots, but there was just not enough evidence right now.

DR. MOCK: Curtis Mock. While it's exciting and it sounds as though there may be great potential, there's just no evidence to support the request of what we're being asked to address today.

DR. ROSENBAUM: Sometimes you say that everything's been said but not everyone's had a chance to say it, but to that I would say I think it's incredibly important to our patients and ourselves as physicians to have a biomarker like this available and so it's, the question is really, this one and now, not whether we need it. And in fact I was moved by the stories, the examples of where it was very helpful, and I'm a big believer in the starfish fable or metaphor, you know, for that one it matters, and the philosophy that one individual is the value of the whole world in some ways, so I found this a very challenging and very

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difficult process. And I was moved, Dr. Foster, by your describing the job of the physician to have the information and tools and to make your best use of it.

That said, in the end I felt very constrained by the question, which is sort of

very different than, you know, if I'm sitting there in the office with my patient or, you know, what I want for a family member. But the question really asked about evidence and a particular type of evidence and that's, I think it really determined my vote as a two.

DR. SANDERS: Amy Sanders, and I am the lone four, and I was primarily persuaded by the patient-centered outcomes idea and the expressions of, from the various panel members about how physician behavior would change in the overall gestalt of how one manages a patient with, especially in the MCI positive versus MCI negative, and those are decisions and forks in the road that I think have potential to have longstanding distal implications for patients' quality of life.

DR. ZEMAN: Bob Zeman. I voted three. I agree with what Amy just said, actually, and

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that's why I voted more than 2.5 basically, because I felt that the broader sort of interpretation of outcomes as they relate to the family unit and to the need to know whether the patient in fact had their cognitive impairment due to Alzheimer's through this amyloid imaging is indeed important. I must admit, I hoped that we would see a little higher score so we could have a discussion around a coverage with evidence development to try to move this up to the Thornbury-Fryback scale a little bit to get it into the diagnostic action category. The Grundman study I think influenced me, but there was still a lot of questions that I really couldn't answer based on that, and so it does seem like this might be one that's off to a CED type of approach to try to gather more data on change in management and what happens longitudinally to the patient. Once you image you cut back on additional diagnostic testing once you have an answer based on the amyloid scan. So I think for all those reasons I voted a three, but really couldn't go much higher in terms of some of the chain of evidence kinds of

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issues.

DR. REDBERG: At this point I reassure you that our fourth voting question is to discuss the evidence gaps and to suggest future studies, and we will have that opportunity.

DR. SEAL: Brian Seal. I voted a three. The coverage with evidence development I think really screams here because we have

some information, the process is very well done to rule out a negative diagnosis, but the idea of intention to change as opposed to actual change is tough to get your hands around. So you know, if we had some actual change, be it a PRO, be it a caregiver, be it a change from position of what they actually did compared to what they did before, it would be very helpful.

DR. HERSCOVITCH: I voted a four. The ability of this test to detect amyloid has been validated against the standard of truth, and in fact that was the basis for the FDA, another government agency, approving this agent. So I think this radiopharmaceutical does work for what it is purported to demonstrate, and that is the presence or absence of amyloid, it is

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not a dipstick test for diagnosing Alzheimer's disease.

Secondly, I was swayed by the data on change in management, partly by the Grundman paper and partly by the testimony we heard, and so the question is for outcomes, it would probably be better to see change, actual change in management, not intended change in management.

So given those and some of the other comments which I agree with, I must say I would have voted a three and perhaps this wasn't quite right, but we didn't really get a chance to discuss it, but I was swayed to a four by this Medicare statement that they consider the evidence adequate that FDG-PET improves health outcomes, and given that and the fact that a lot of analogies can be drawn between the type of patient that decision was describing and where amyloid PET might be used, I did nudge it up to a four.

DR. REDBERG: Thank you.

DR. LYKETSOS: I will be brief. I focused on the word adequate evidence, I was trying to decide what that meant, and I was

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swayed by the precedent that CMS has set that was just quoted. I think it's going to be very difficult for me to understand why a new precedent will be set for a very similar diagnostic circumstance for a test that actually has much better evidence than FDG-PET had at the time.

I think from the health outcome point of view, and speaking now as a clinician who looks after a lot of folks like this, the

examples that were already given are similar to mine. The thing that really drove it for me is that if you have MCI, and we can define it, we know what it is, you have a very different prognosis if you have a positive scan or not. Only some of that data was shown. The data shown here related to the Amyvid scan, but there are data with many of the other amyloid scans that confirm it, those data were not shown. So for me, the level of evidence is actually quite good. There are lots of people with MCI, they are pouring into memory clinics right now. This would really change things for millions of people to know if they are amyloid-positive or amyloid-negative, and

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that's really what drove it for me, that would be enough for me to get the test.

DR. REDBERG: Okay. Thank you all for your comments and we'll have two more voting questions and opportunity for further discussion. So, the next question is: How confident are you that these conclusions are generalizable to the Medicare beneficiary population, and it would be the same voting scale, one would be low confidence and five would be high confidence. That would be the conclusions you just made.

DR. COZZENS: What conclusions are we talking about?

DR. JACQUES: Louis Jacques again. If you've essentially concluded that, depending on how you voted, that there either was or wasn't enough evidence to sort of consider the dispositive question of does it improve health outcomes, do you feel that that conclusion itself always applies to the Medicare beneficiary population. And the reason why that's an important nuance, much of the evidence that was discussed was discussed around a patient population that was not yet

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eligible for Medicare status, aside from those who may have been permanently disabled earlier. We heard a lot of commentary about people in their 40s, people in their 50s, people in their early 60s. As Medicare deals with this issue we will be dealing in general with patients who are 65 or older, although there certainly are others. If you or any other committee member feels that that difference itself is meaningful in some way, then we just invite your comment on that.

DR. FENDRICK: Point of procedure. Is

agreeing with the prior vote a five or -- this comes up every time. If you agree with the prior vote, is it a five even though the vote was -- say you voted a one, and you believe that the data are equally great or crappy in Medicare relative to the general population. Do we vote one or vote five?
DR. JACQUES: Five.
DR. FENDRICK: Last time it wasn't five.
DR. SEDRAKYAN: If it's highly generalizable, then it would be five.
DR. FENDRICK: So if you think that

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Medicare is different than your answer on one, then you vote a low number?
DR. JACQUES: Yes. If you think that your conclusions apply to the Medicare population, vote a five.
DR. FENDRICK: Equally good or bad?
DR. JACQUES: Yes.
(The panel voted and votes were recorded by staff.)
DR. REDBERG: Okay. So, I think the panel is highly confident that these conclusions are generalizable to the Medicare beneficiary, and the vote was a mean of 4.25, with most panel members, seven voting high confidence, two voting four or intermediate to high, two voting intermediate confidence, one voting intermediate to low confidence. And so again, we'll go down and state your vote, and you can discuss it.
DR. SEDRAKYAN: I was highly confident that what I said is definitely applicable to the Medicare population. And again, it goes back to the same questions that we highlighted before, inappropriate use reduction, we heard from presenters that there's no harm trying

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Alzheimer's medications on people who didn't have Alzheimer's but there's a lot of elderly people who have some sort of cognitive decline, so I don't see that reduction itself is a big volume, particularly as we move towards an older population.
And then knowing, which is important again, versus elderly populations, certainly as Dr. Redberg alluded to, the sensitivity and specificity issues are less clear, they are more likely to be lower, and the false positive rates is more likely to be higher. So again, people who will be informed they have Alzheimer's but they might not have it, the

proportion of those people is going up again and needs to be weighed with the patients who learn that they have Alzheimer's over 65, and they need to do the planning. So again, the balance in how I voted two gets even stronger favoring the two than I was.

DR. COZZENS: Jeff Cozzens. Again, I think that the studies that have been done have focused mostly on the Medicare population and there were a few outliers, but most of them were either the Medicare population or they

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could be generalized easily to the Medicare population, so I voted a five.

DR. FAUGHT: This is Ed Faught. I voted a four because there may be some differences if we stratify people by age between the specificity and sensitivity of this test, and especially the MCI in younger people and older people.

DR. FENDRICK: Mark Fendrick. Regarding health outcomes, the absence of evidence is not evidence of absence, and I want to thank all of you for the dedication and the work that you've done, and I really do believe that there would be a path to move forward to answer some of these questions and reduce our lack of confidence over some of these things.

DR. GUTMAN: Yeah. The study that I'm so uncomfortable with which is study two in the FDA submission has an average age of 83, so I assume that is probably a good proxy for the Medicare population.

DR. HARTMAN-STEIN: I voted five, meaning high confidence that I question the health outcomes for this population, especially because I think there's even a greater risk in

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this population of overpathologizing people who might have a positive scan, but again, many of them are going to have positive scans, and so people who maybe are positive, every time they make little misses they're going to really think the worst, so I even have more questions about it with this population.

DR. LEVINE: Susan Levine. I voted five because I also feel that there is lack of evidence in the Medicare-aged population as well as other populations.

DR. MISKIMEN: Theresa Miskimen, I voted three. I thought that now because of the Medicare population, the fact that they would be coming in more with cognitive deficits, if you do have a positive test, then that would

give me more confidence just based on some of the literature which I read, and that's why I voted a three.
DR. MOCK: Curtis Mock, I voted a two, and I think, I was clear on what the question was asking. I'm not confident that the conclusions that we heard today are generalizable to the Medicare beneficiary population. Now if that wasn't the purpose of the
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question, then no, I didn't answer it correctly. So let me state that in the interest of the triple aim, I certainly think that we want to be standing on evidence and not standing on what we think might happen. So if that is what the question is asking, then I answered it appropriately as I think, which is two, I'm not confident that the conclusions that we heard today are generalizable to the Medicare membership.
DR. ROSENBAUM: So, I was intermediately confident, and I think it was the difficulty getting my head around the sensitivity and specificity issues of a population that will have more amyloid and have more Alzheimer's, so I wasn't sure how generalizable. But also, the discussion about what we're really trying to convey was a blow to me a little bit.
DR. SANDERS: Amy Sanders. I voted a five because I think that the evidence is that many of the studies were done in people who had an average age that we consider to be in the Medicare population.
DR. ZEMAN: This is Bob Zeman, I voted
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a four. I am pretty confident that it is generalizable to the Medicare population. We heard a number of folks today talk about their typical MCI patient being in the 60 to 70-year-old age group, and I also just looked up the statistics, the distribution of ages in the Medicare system. 17 percent in 2011, correct me if I'm wrong, Louis, are patients under the age of 64 or less, fall under the Medicare system largely because of disability. So again, it is a little bit of a heterogeneous group in terms of age also.
DR. SEAL: Brian Seal. I voted a four as well. These dealt with mostly Medicare patients today, and if not, they're going to be the Medicare population tomorrow. So if you're 60 today, you're going to be in the Medicare population in a couple years if you're still

alive.
DR. HERSCOVITCH: I voted four as well for similar reasons. Perhaps the only concern is that many of the studies are perhaps, it might be good to have additional studies where you have more of a mixed category of patients, more routine clinical practice of dementia

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clinics, more routine nuclear medicine clinics. Lots of these studies were very well done, so perhaps the populations were somewhat selective, so I voted four rather than five.
DR. LYKETSOS: I voted five. The vast majority of research about MCI, positive and negative scans predicting conversion to dementia is in folks who would be or were Medicare beneficiaries.
DR. REDBERG: Great.
MS. ELLIS: I'm sorry. Could Dr. Gutman and Dr. Rosenbaum, could you please state your score again, please.
DR. GUTMAN: Yeah, my score was five. I'm sorry.
DR. ROSENBAUM: Three.
MS. ELLIS: Thank you.
DR. REDBERG: Thank you. And to just start the last question which is not a voting question, it's a discussion question, I first wanted to again thank all of the speakers because you really set the stage for the discussion of the next question, which is really what are the current evidence gaps and what are the types of clinical studies, and you

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clearly have all contributed, not just to the research but to the clinical care of patients with Alzheimer's, and I and all the panelists are grateful for you sharing your knowledge with us today.
The fourth question is, please discuss any evidence gaps and the types of clinical studies that would be needed to confidently close those gaps.
I'll just start out by stating the ICER paper that Steve's group has summarized does have a list at the end and we could go through some of those, although I will let the panelists start. The only one of those I wanted to note is the issue that I think comes up frequently in clinical trials in the Medicare population is that we often have for many reasons many inclusions and exclusions in clinical trials that we obviously don't have in the Medicare population, we take care of all

comers. And so I think having data on more patients that have comorbidities, complicated situations may be very helpful to inform Medicare decisions. And I'll open it up now to Dr. Gutman and to Dr. Cozzens.

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DR. GUTMAN: I think that at least what I see as a flaw here is the belief that you can take the FDA data which is based upon a population that is largely patients who have clinically diagnosed AD and a fairly substantial minority, 20 percent who are cognitively fine, and extrapolate that into something that tells you about patients with the persistent threat of unexplained MCI. So I would plead for, if what you're interested in is unexplained MCI, that you have at least 59 patients studied in patients with MCI, so you really know what the sensitivity and the specificity are. If you had confidence in the sensitivity and specificity, I do think you could construct the chain of evidence that you're trying to construct. I just think it's a house of cards and you don't have the lower layer.

DR. REDBERG: Dr. Herscovitch.

DR. HERSCOVITCH: Just to make a comment with regard to chain of evidence, that the FDA study, it's my understanding of it that it was, looked at the test in terms of its ability to detect the absence or the presence

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of amyloid, that being, though, a hallmark of the pathological diagnosis of Alzheimer's. Many of the patients had a spectrum of dementing diseases, but this wasn't at least tested by the FDA as an exam for the presence or absence of the diagnosis of Alzheimer's disease. So in terms of chains of evidence and how this might be used clinically, I think the starting point should be what the FDA agreed was validated, and that was as an amyloid imaging agent, not as an Alzheimer's detection agent.

DR. REDBERG: Dr. Cozzens.

DR. COZZENS: Jeff Cozzens. I have no doubt that it detects amyloid, as it's intended to do. I think that if further studies need to be done, you could do brain biopsies on these people, and I'm happy to participate in those types of studies if necessary, because I think there's enough equipoise that you could do that ethically to do a brain autopsy. You don't have to wait for autopsy.

I don't think those studies are necessary, though. I think you need more data like in the Gunderson, and I may have the name wrong --

DR. REDBERG: Grundman, I think. The one where they asked doctors what would you do?

DR. COZZENS: Yeah, the one where they asked doctors what they would do. But I think that where they looked at the change in management, I don't think it should be theoretical change in management but the actual change in management. I would like to see Medicare cover this for patients who are enrolled in a clinical trial, I think that would encourage more studies, and I think that would be very helpful to encourage more studies.

DR. FAUGHT: This is Ed Faught. I certainly agree with the comments, it's going to be mostly useful in these populations that have been refined by the recommendations of the panel. I think that was, the largest one would be MCI, and then you've got atypical presentation and atypical age, and so we need more patients in those kinds of hard to diagnose groups, to be sure. This question about what the impact of the diagnosis is on people is fairly important and I think, I'm not usually a big advocate of quality of life studies, but I think this is a place where it could certainly be applied. You know, what difference does it make to people, let's find out, and do people want to know.

DR. REDBERG: And I would just add, and then Dr. Zeman, that I do think, as was raised earlier, that the quality of life should include the family because there is a big impact, I think, on caregivers and people who take care of patients with Alzheimer's. But I do think, you know, having data from randomized controlled studies that actually tell us how patients actually do and how doctors actually use the information would be extremely helpful, because what doctors say they're going to do is not as useful, as Mark said from behavioral studies, so it would be very helpful. Dr. Zeman.

DR. ZEMAN: That's why I basically brought up the CED approach earlier, because it's a perfect vehicle for collecting some of this data on what the change of management is and to follow patients longitudinally. I

really thing the difficulty is that
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particularly when I think about the early days of the PET registry for oncologic PET, is that most of our clinicians did the filling out the forms in the beginning, it got older and older and when they had to keep doing it over the years, and now there's so much more private insurance reality, benefits managers have acquired preauthorization in peer-to-peer conversations, and the clinicians are just getting overwhelmed in my institution either having the preauthorized studies or filling out forms for PET registries and things like that. So I'm a little concerned about how something like that would be met and would be implemented, but it certainly would allow us to collect more data.
DR. REDBERG: And I'm sorry to ask you, but since you brought it up, Dr. Zeman, how has the data from the PET registry been used to inform future clinical practice? Has there been publications?
DR. ZEMAN: Yeah, there's been publications, and I'm sure that other members here could comment on it, but there is publication in the Journal of Nuclear Medicine
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in particular, and some of that has obviously been cut back to CMS, which I think has generally viewed the data they've gotten back as relatively productive data, and Louis could probably comment on that.
DR. JACQUES: I would just comment that Bruce Sellers, who stood up in the back, is the principal investigator on much of the NOPR things, so if anybody wants to have a conversation with him, probably after the meeting, he is there.
DR. REDBERG: Dr. Seal.
DR. SEAL: I was just going to say the same piece around coverage with evidence development, because there's a lot of questions I think the panel has, both from patient-reported outcomes and changes in medical plans, but also the specificity of the tests themselves, it could all be incorporated into the same study, so you could answer a lot of things and be able to follow the patients longitudinally and see what happens over the years.
DR. REDBERG: Thank you.
Dr. Lyketsos.
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DR. LYKETSOS: I'd certainly like to see more research that compares different diagnostics in different settings, so in MCI, how does Amyvid imaging compare, say, to neuropsychological testing in terms of the patient outcomes that we're talking about, and the same in the various atypical dementias that we talked about. I think that comparison will be helpful both in the is one better than the other assessment point of view, but also to be able to incorporate cost questions down the line, whether certain things are more worthy of payment.

DR. REDBERG: Dr. Miskimen and then Dr. Sedrakyan.

DR. MISKIMEN: I thought that the ICER article actually had a wonderful foundation for research, and I would like to see more research in terms of the MCI with the progression with and without the amyloid, and I think that would definitely take it that next step and would answer some of the questions that we were having about what exactly is it that we were doing and what is it that we're telling our patients. So I think it would inform the

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clinical person that's having to deal with this on a day-to-day basis, which is what actually we have been hearing, that frustration, what is it that we're telling our patients, how is it with their families, and how is it that they're actually taking in the information. So definitely start with the research, and it's fantastic.

DR. REDBERG: Dr. Herscovitch.

DR. HERSCOVITCH: I would concur with that, coverage with evidence development would help fill in a lot of very substantive questions that many of the panelists raised and in addition to the some of the suggestions, perhaps there should be consideration, should this be covered in such a manner, of the accuracy of physician interpretation as the test would be moving beyond more academic research centers as part of the studies, that should be considered as well.

DR. REDBERG: Dr. Sanders.

DR. SANDERS: I think it would be interesting to see to what extent a new class of health disparity is created if there is not coverage for this. Is the, was it the cleaning

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lady and the high school principal going to be people who are not going to get this

information, yet the corporate CEO who can pay for it out of his own pocket is going to have a benefit of this information.

DR. REDBERG: Again, I think it's really important to focus on outcomes and so, you know, I think test disparities are important if they impact outcomes, and so I think what we first need to start out in any field, and this one certainly, is randomized clinical trials. And certainly when there is a demonstrated difference in outcomes in people who have amyloid scan as part of their diagnostic testing for Alzheimer's dementia and people that don't, then, you know, I would be concerned about disparity. At this point from the data we saw, I think that would be the data we need first before we can get to the other question.

My understanding is there are studies beginning at this time, and some of them NIH-funded. I don't know if anyone else wants to comment on what is currently ongoing, but one of the many articles I read listed about

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four or five studies at the end that had been studied. I was encouraged when Steve said there was postmarketing surveillance, following the patients that have already gotten the scan and looking at outcomes in the real world, so I think that's most helpful after you've had the randomized control trial data because you don't have a control group when you just have a following of people who got the scan, but it does tell you what happened afterwards. Yes, Dr. Hartman-Stein.

DR. HARTMAN-STEIN: Paula Hartman-Stein. I just want to echo what several panelists have said about quality of life and the need to look at that, and the societal implications. Again, especially in the Medicare population, older adults, again, if they are told they have a positive amyloid scan but they have MCI symptoms, how does that, you know, we may believe that, but I'm not sure it's absolutely a hundred percent sure, that if you have an amyloid scan, that said that you have Alzheimer's disease. So if it isn't a one-to-one correlation, then what is the societal implications for the people who are

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told that they probably will? I mean, on how the family treats them, you know, just the number of societal things, it's so vast a question, and I'm not sure how the research

will be done, but it needs to be looked at before this is done widespread.
DR. REDBERG: Dr. Cozzens.
DR. COZZENS: Jeff Cozzens again. Yeah, there seems to be some disagreement about whether there was a one-to-one correlation about presence of amyloid and whether someone was guaranteed to develop Alzheimer's disease or not, and I think further studies might help to answer that.
DR. REDBERG: Okay. Again, I think this is really an important issue. As everyone here agrees, Alzheimer's is certainly a growing problem and a really important problem that has a tremendous impact on our patients, mostly on quality of life. I think that it's something that, even though, as I said, I'm a cardiologist, it's very frequent that patients come to my office and tell me about their memory loss. And quite frankly when I read the, you know, forgetting your keys, how many

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people in this room have forgotten their keys? You don't have to answer that, but it is a very important problem, and I think we really all embrace resurgent evidence on how to take better care in diagnosing and treating and improving outcomes in patients with Alzheimer's.
I again, I want to thank the panelists, I want to thank the CMS, Dr. Jacques and Maria Ellis for organizing this, Dr. Hutter and Dr. Rollins, all of the guest speakers. And I think, unless Louis wants to have a final word --
DR. JACQUES: That's the only good thing about this job, I get the final word. Thank you all for coming, I do sincerely appreciate your attendance. We tried, especially with the guest speakers, to get the people who know the most about this subject.
I do want to let you know, there's an awful line of weather between here and Pittsburgh. Thunderstorms are scheduled here in the next couple of hours. Looking at the app on my phone there are significant weather

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delays in Atlanta, Newark, JFK, LaGuardia, O'Hare and Philadelphia. On that note, please travel safely, we do want to see you again, and we are adjourned.
(Whereupon, the meeting adjourned at 3:09 p.m.)

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