

Centers for Medicare & Medicaid Services  
National Coverage Determination Analysis for Monoclonal Antibodies that Target  
Amyloid for the Treatment of Alzheimer's Disease  
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To access the call audio:

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**Stefanie Costello:** Good morning. And welcome to the National Coverage Determination Analysis on Treatment for Alzheimer's Disease listening session. I'm Stefanie Costello, Director of the Partner Relations Group in the CMS Office of Communications and I will be moderating today's listening session. Today I'm joined by Tamara Jensen who is the Director of the Coverage and Analysis Group in the Center for Clinical Standards and Quality. Before we begin, I have a few housekeeping tips.

This call is being recorded and will be transcribed to serve as an official record as part of the National Coverage Determination or as you will hear it referenced here NCD.

While members of the press are welcomed to attend the call, please note that all press and media questions should be submitted using our media inquiries form which may be found at [cms.gov/newsroom/media-inquiries](https://www.cms.gov/newsroom/media-inquiries).

Today's listening session is an opportunity for CMS to hear public comments. As such, we are not gathering written comments or taking questions through the Zoom platform.

We will also not be responding to the comments made or answering questions asked during the comment portion of the call. All written comments must be submitted to the NCD tracking document. A link to the tracking document is appearing on the screen, and will be up for the remainder of today's session.

The list of today's speakers was compiled based off those who indicated through the registration process that they wanted to speak on today's listening session. We will

do our best to get to as many speakers as possible. Each speaker will have approximately 3 to 5 minutes. We're keeping an eye on the time, and we'll politely ask those speaking to finish remarks on time.

And with that, I will turn it over to Tamara Jensen, the Director of the Coverage and Analysis Group in the Center for Clinical Standards and Quality. Tamara?

**Tamara Syrek Jensen:** Thank you, Stefanie. Good morning, everyone. And thank you all for joining our listening session today. Again, my name is Tamara Syrek Jensen and I am the Director of the Coverage and Analysis Group in the Center for Clinical Standards and Quality. As many of you know, aducanumab, or the brand name Aduhelm, was recently approved by the FDA. CMS has initiated an NCD analysis to examine whether Medicare will establish a national coverage policy for Aduhelm. This NCD analysis will also include any feature monoclonal antibodies directed against amyloids with an indication in use for treating Alzheimer disease. Aduhelm is currently the only monoclonal antibody directed against amyloid-beta approved by the FDA for the treatment of Alzheimer's disease. By engaging in the NCD process, CMS will determine whether the evidence supports improvements in health outcomes of adding Aduhelm as a national coverage treatment option for beneficiaries.

The public process for NCDs remains a CMS cornerstone. CMS follows a longstanding process developed by Congress to determine whether a medical item or service can be covered nationally by Medicare. This includes whether an item or service is reasonable and necessary for the diagnosis of, and/or treatment of an illness or injury. NCDs are made through an evidence-based process that includes multiple opportunities for public participation. CMS developed NCDs using all relevant published evidence and feedback received from all stakeholders.

The NCD process is open and it is critical that stakeholders provide input. We are listening to all feedback received. Through the NCD tracking sheet, CMS will continue to provide ongoing communications and updates to keep the public informed. Our goal at the end of this process is to provide the American public with clear, trusted, evidence-based decisions that has been a -- that has been through a thorough evidentiary

analysis for Medicare beneficiaries. The NCD process begins when the CMS announce an item is under consideration or posting a notice or commonly referred to as a tracking sheet on the CMS coverage website and you can see the link displayed currently.

CMS posts a specific tracking sheet for each item or service under review. The tracking sheet may include questions or issues the agency wants stakeholders such as medical societies, clinicians, researchers, patients, family and caregiver advocates, as well as the general public, to specifically comment on during the 30-day public comment period.

For this specific NCD, the initial public comment period ends on August 11<sup>th</sup>, 2021. CMS carefully reviews all comments and associated evidence to develop the proposed NCD and the decision memorandum. The memorandum contains an analysis of evidence that supported CMS's NCD conclusion. This phase of the process typically takes six months. CMS expects a proposed NCD and decision memorandum to be published no later than January 12<sup>th</sup>, 2022.

Once the proposed NCD is available, the public has another opportunity to provide comment. This is the second 30-day public comment period. To ensure complete transparency, public comments received are posted on the CMS Coverage Group's website.

Typically, a final NCD is available 90 days after the proposed NCD is published. The final NCD and decision memorandum are posted on the CMS coverage website with the NCD effective on the same day that we publish it. Therefore, a final NCD would be completed no later than April 12<sup>th</sup>, 2022.

While the NCD process is underway, the Medicare contractors representing 12 jurisdictions across the country will continue to make the decisions regarding coverage for Aduhelm on a case-by-case basis, using all available evidence. Please note that Medicare payment rate and coding are developed outside of this NCD process. As Stefanie mentioned today -- as Stefanie mentioned, today's listening session is an opportunity for CMS to hear public comment and we will not be responding to the comments made or answering questions asked during the comment portion of this call.

Again, we appreciate your feedback and we look forward to hearing from all of

you. Thank you. Stefanie?

**Stefanie:** Thank you, Tamara. And now we will begin the listening session portion of the call. I will call on individuals and you will be unmuted to make your comments. Again, comments should be held 3 to 5 minutes and with that, I will call on those who have signed up to speak and the moderator will be unmuting your phone. First up, we have Maria Carrillo from the Alzheimer's Association.

**Maria:** Thank you very much. Can you hear me?

**Moderator:** Yes, we can hear you, Maria. Thank you.

**Maria:** Thank you very much. I'm the chief science officer for the Alzheimer's Association and on behalf of all of those living with Alzheimer's and their caregivers, and their families, I want to thank you for the opportunity to address you today and the CMS Coverage and Analysis Group. I want to thank you particularly for being such a valued partner on the imaging dementia evidence for amyloid scanning and IDEAS study and of course the new IDEAS study which is addressing underrepresented populations in terms of studying amyloid scan and impact on diagnosis and further, of course, health outcomes.

We're very grateful for our partnership with the CED programs and before I go on, I would like to announce that our disclosures at the Alzheimer's Association are the following: we've received 0.89% of our total contributed revenue from the biotechnology pharmaceutical diagnostic and clinical research industry, including 0.5% from Biogen and Eisai 0.15%. This can be found at [Alz.org/transparency](http://Alz.org/transparency).

The Alzheimer's Association strongly urges the Centers for Medicare and Medicaid Services to issue a favorable National Coverage Determination and make this and future Alzheimer's therapies available to all individuals who have the potential to benefit. As the leading voluntary health organization in Alzheimer's care support and research, each year we speak with hundreds of thousands of families through our 24/7,

365 days a year help line and serve hundreds of thousands more providing access and direct support across the country.

Through our work, we see firsthand the devastating toll of Alzheimer's and what it takes on individuals, their carers and their families. I have lost two family members to Alzheimer's and related dementia in the last four years and know this myself personally.

As all of you know aducanumab is the first of several treatments in this class, and I'm glad you are considering this as a class. It is first treatment to be approved for Alzheimer since 2003 and the first ever to address underlying biology And the FDA specified the treatment should initiated in patients in patients with Alzheimer's disease in stages at which they were studying the trials, that's mild cognitive impairment (MCI) or mild dementia stage of the disease. Aducanumab was studied in these populations and showed that evidence of the buildup of plaques in the brain could, in fact, provide a reasonably likely important benefit to those patients.

The population indicated in the FDA label is what we agree should be the one that can potentially benefit from treatment and who should be approved for reimbursement through CAG and CMS. This potential for benefit, though modest and not a cure, we understand, can be incredibly significant, considering the early signs of Alzheimer's disease that the evidence indicates, again a reasonable likelihood of benefit. Being able to stay in the mild cognitive impairment due to AD or early dementia stage for months or longer is something anyone who has experienced this devastating disease would want for their loved one, more time to enjoy, what time is actually meaningful. That time is priceless. And it's so important when there is no way out. Every single person with -- who receives a diagnosis of Alzheimer's disease will die with it or of it.

And as you consider coverage, we must of course consider the racial and ethnic populations that are disproportionately impacted by Alzheimer's and other dementias. Historically again also through what we understand are the social determinants of health. Older blacks are twice as likely to have Alzheimer's or other dementia than whites, and older Hispanics are about one and a half times likely. We refer CMS and CAG to our 2021 report on race, ethnicity and Alzheimer's in America. A key finding is that discrimination remains a huge barrier and we are committed to eliminating all barriers as

an organization and we are committed to supporting CMS towards its own efforts to that end.

So, this is the first of the new treatments to come. I will finish off by just saying history has shown approvals invigorate the field and that is very important because we do know there's a pipeline. And again, very pleased that this consideration is broadly for the class. New treatments will become available in the coming few years. We know they are in the pipeline and The Association is committed to supporting CMS in making coverage decisions and removing barriers to those treatments for all individuals who have the potential to benefit, including those populations disproportionately affected by this disease and who have been historically underrepresented and left out of healthcare.

The Association is grateful to CAG for all of your careful consideration and the evidence that you will be gathering and thank you for the opportunity to comment.

**Stefanie:** Thank you very much. Our next speaker is Sue Peschin from the Alliance for Aging Research.

**Sue:** (Silence).

**Stefanie:** Sue, I believe you need to unmute yourself as well. Moderator, can you please unmute Sue Peschin

**Moderator:** Yes, I have. She needs to unmute on her end.

**Stefanie** We'll come back to Sue, she might have stepped away. Our next speaker is AJ Rice with Credit Suisse.

**Moderator:** I don't see him.

**Stefanie:** Okay. Thank you. Our next speaker is Ian Kremer from Lead Coalition. The Leaders Engaged on Alzheimer's Disease.

**Moderator:** He's not coming up.

**Stefanie:** So Ian Kremer is not on either? All right. Let's circle back and see if Sue Peschin is ready to speak. We can hear you Sue, go ahead.

**Sue:** I am so sorry. My mom, actually, called me. So I apologize. I stepped away. Hi, everybody. So my name is Sue Peschin and I serve as President and CEO for the Alliance for Aging Research and I really appreciate the fact that CMS is doing these stakeholder calls. I do have one request for the Coverage and Analysis Group, just for the next stakeholder call on July 27<sup>th</sup>. I realize you guys are incredibly busy, but I just ask that you please adhere to the 24-hour notice for folks who are participating in the next call to let people know that they are up for public comment. I didn't get notified until 10:00 last night. So that's just one thing to keep in mind for the next call. My second request is the regarding CMS's coverage for the treatment under discussion during the NCD process.

My understanding is that patients are currently being denied coverage at the local MAC level and I ask that CMS please work swiftly with the sponsor company to determine coverage for the next 9 to 12 months as you have done with other medical products under NCD discussion. Cause right now, I think every -- all the payers are left hanging and making decisions left and right not to cover. And then a couple of quick things around the process for this. I'm sure you saw, former CMS administrator, Mark McClellan, it would be unusual and the Alliance would argue, ethically questionable for CMS to require its own separate randomized coverage with evidence development study on a drug where the indication has been approved by the FDA under accelerated approval. There's also other randomized trials that are underway by other sponsors for the same types of treatments and those will be reading out in the coming months. So I don't think CMS needs to duplicate on that.

I know it's been suggested to do an observational registry-type approach as you have done with other coverage with evidence development decisions. But we have had

experience as CMS knows with other coverage with evidence development processes for devices used to treat heart valve disease and as a result of that experience, we have a couple of points to raise and just hope that is, you know, this can learn from those experiences. We would like the registry under the CED, if it is a CED, or under the NCD to basically say that it has to be strictly focused on answering the evidence questions that are raised by CMS and no other types of questions from other academics or others who want to do studies to prove by certain providers should be doing this, or volume requirements or any of that.

It should be subject to timelines for CMS, and those should be specified in the coverage decision. We would also like the registry stewards to publish an annual report on the data that's collected, in a peer-reviewed publication that offers open access so that patients and families can see up-to-date results of the study to help with their treatment decision-making.

And then we would like any type of charges by the registry stewards to be transparent, and not be more than, you know, a slightly above the cost to run the registries because it does otherwise restrict to larger academic centers and it prevents smaller hospitals from being able participate and to your points on wanting to help with equity issues we think this would go a long way. We also think that it's very important that the process for what people are asking for in terms of the design of the coverage decision- who gets to give the treatment and where the treatment is given -is provided along the way so it's not just released in a draft comment format, but the questions are raised along the way so people can actually comment on those.

Because when this is done in just sort of a "here's a consensus statement, and CMS is just going with the consensus statement process", it leaves little room for any type of revision. And we would like to see this be a bit more -- (Audio drop) and last, I think that the point around making sure there's a beginning, middle and end to this process. Once it's decided, not -- not for the NCD process but for the study period itself, the observational study period that that be made as clear as possible. Because we've seen it with PET, how it has dragged out. We're told we are waiting for publication. Publication has occurred. It's continued to be drawn out. So please be as transparent as



possible about the timelines. The patients and the families deserve it.

These CEDs with in our experience with TAVR and TEER, they can sometimes perpetuate inequities because when it's at the large academic centers, it's not as easy for communities of color to receive access. And it's 3 to 2% for Blacks and for Hispanics with those products and I imagine it will be about the same with this if it's relegated to that and specialty societies come in and they do their kind of territorial thing. I ask you to be cognizant of all of those issues and to try to get this done as quickly as possible. Thank you so much for the time.

**Stefanie:** Thank you. Our next speaker is Robert Kinyua from Prime Therapeutics.

**Robert:** (Silence).

**Moderator:** Robert, you need to click the unmute.

**Stefanie:** Robert Kinyua

**Robert:** You have the wrong Robert that you're trying to unmute.

**Stefanie:** Robert Kinyua.

**Moderator:** He's not coming up.

**Stefanie:** The next speaker is Max Linder.

**Moderator:** No Max Linder.

**Stefanie:** Up next, we have Patricia Bencivenga

**Moderator:** Yeah, I got her.

**Stefanie:** Great. Patricia, you can go ahead and unmute.

**Patricia:** Good morning my name is Patricia Bencivenga and I'm a graduate student in Georgetown University's health and the public interest master's program. I'm currently an intern for and representing PharmedOut, a Georgetown University Medical Center program that advances evidence-based prescribing and that educates healthcare professionals and students about pharmaceutical and medical device marketing practices. We ask CMS to refuse all coverage of Aduhelm and any other drugs approved only on the basis of reducing amyloid plaque.

My response addresses questions 1 and 3. Question one, regarding important health outcomes. A treatment for Alzheimer's patients should improve cognitive function. Ideally the result would be restoration of loss function, however, the sensation of the client is also a meaningful outcome. important. The target outcome is to improve cognitive function, memory, daily function, independence, productivity, communication, and enjoyment of life. Also, treatment benefits should be durable, and benefits should far outweigh the harms. Aduhelm fails in all of these regards. It does not restore or improve cognitive function.

It does not stop decline and it has a clinically inconsequential effect on delaying decline. Also, it has an unacceptably high rate of adverse events. Up to 40% in the high dose group from the trials experience brain swelling or brain bleeding, termed misleading ARIA. Biogen recommends discontinuation of treatment after 10 bleeding events. So it should come as no surprise that the bleeding events cause cognitive decline. Patients with brain swelling or bleeds experience headaches, visual disturbances, nausea, dizziness, confusion, disorientation and altered mental status. These symptoms will not improve patients' lives. The fact that some adverse events including disorientation and confusion can't be easily differentiated from disease progression is highly problematic. Aduhelm is not benign. Patients who may have remained stable without any treatment may experience harm from this drug. No drug for dementia should be approved or paid for on the basis of amyloid plaque reduction because reducing plaque isn't associated with

reducing symptoms.

Now on to question three that asked about issues of equity and inclusion. It is critical to have equity and inclusion in clinical trials and drug companies should not be able to sell or advertise drugs to people of color or any minority group who are not included in the clinical trials. Combining patient population in both the emerged and engaged trials, Biogen included 19 Black participants. That's less than 1%. Also, only 104 or 3.2% were Latinx. Equity shouldn't be about equal access to ineffective and harmful drugs, especially when that drug was not tested in the population it's aimed at. Unproven benefits and proven harms are a bad combination. We urge CMS not to cover Aduhelm in any population. Patients and their families need effective therapeutics not false hope. Refusing to cover this drug in any population would be the best course to protect patients from the harmful effects of this drug. Thank you.

**Stefanie:** Thank you very much. Our next speaker is Eilon Caspi from the University of Connecticut.

**Moderator:** Not coming up.

**Stefanie:** Okay. Moving on. Our next speaker is Adriane Fugh-Berman

**Adriane:** Good morning. My name is Adriane Fugh-Berman, I'm a physician and professor in the Departments of Pharmacology and Physiology in the Department of Family Medicine at Georgetown University Medical Center where I direct PharmedOut a research and education program that promotes rational prescribing. Aducanumab should not be covered by CMS because it doesn't work, it hurts people, and it has the potential to drain the resources of payers. Many drugs have been shown to reduce amyloid plaque, none of these, including aducanumab have shown a clinically significant benefit. None of the 25 trials of drugs that reduce plaque in Alzheimer's patients has been successful in treating the disease. Plaque doesn't indicate future decline either. The connection between Alzheimer's and amyloid is unclear and the majority of people with amyloid

plaque never develop dementia. One study that followed normal elderly people for up to 16 years found that those with plaque and pathological brain changes typical of Alzheimer's had the same risk of cognitive decline as those with no brain changes.

The goal is not to help plaque. The goal is to help patients. Not only are amyloid targeted drugs far from benign, they sometimes worsen the condition they are meant to treat. 40% of aducanumab patients will experience brain swelling or brain bleeds which are called ARIA-E or ARIA-H. The term ARIA linguistically understates the seriousness of these events. ARIA sounds both benign and musical. It stands for amyloid-related imaging abnormality but really this is drug-induced bleeding or swelling. Burdensome and expensive monitoring includes regular MRIs. Biogen recommends considering halting treatment only after ten bleeding events.

CMS should refuse to cover aducanumab in any population. Biogen and Eisai are already spreading misinformation. Their "it's time we know" website states wrongly that in 1 in 12 Americans aged 50 years or older have noticeable symptoms of MCI and states wrongly that MCI is most commonly due to Alzheimer's disease. Initiatives by Biogen and Eisai are already attempting to scare perfectly normal 50-year-olds into believing they have MCI because of Alzheimer's. The potential target is immense. If CMS covers this drug, elders who occasionally mislay keys will be beating down the door for it.

The FDA erred in approving this drug but CMS has the chance to do the right thing for public health which is to deny coverage for this ineffective and harmful drug. There are already proven and underused measures for delaying cognitive decline, including deprescribing unneeded drugs, treating hypertension, addressing sleep apnea, increasing social interactions and exercise. One RCT for example found elders with mild cognitive impairment, who were assigned to learn ballroom dancing significantly improved compared to a control group.

The Lancet condition had 12 modifiable risk factors that account for 40% of dementia, including traumatic brain injury, diabetes, depression and smoking. The most effective intervention and the one most relevant to CMS is hearing aids. Decreased hearing loss hastens cognitive decline and hearing aids reduce this decline. Hearing aids are an effective, life enhancing, and harmless intervention that Medicare does not cover.

A pair of hearing aids would be less than a tenth of what the first year of Aduhelm costs. Traditional Medicare, not just Medicare Advantage should be covering hearing aids.

There's simply no setting in which this treatment should be given to people. CMS should focus on modifiable risk factors and cover hearing aids and not aducanumab.

Thank you.

**Stefanie:** Thank you very much. Our next speaker is Ian Kremer. Ian, you need to unmute.

**Ian:** Good morning, can you hear me now?

**Stefanie:** Yes, I can. Thank you, go ahead

**Ian:** Sorry for my difficulty coming off mute and thank you for this NCD analysis and the opportunity to speak. My name is Ian Kramer. I'm the Executive Director of the LEAD coalition, leaders engaged on Alzheimer disease. I want to begin by making clear, the comments I offer today represent my views exclusively. They do not necessarily represent the views of the entire LEAD coalition or any of our individual member organizations or allies.

I have been working on Alzheimer's and dementia professionally for almost 25 years and my family intermittently has experienced Alzheimer's disease and other forms of dementia for over 30 years.

I have known thousands and thousands of families and individuals living with these conditions over that time. For me, this is both a professional and a deeply personal set of questions that CMS is posing. And I will start with question number one.

In terms of the most important health outcome -- and there are many important health outcomes, I think they all come back to time. Any opportunity to significantly, whether it's months or ideally years, to delay or slow decline is central to families like mine and millions of families like ours.

Everything else ties to time. The ability to be an engaged decision-maker for all

that will come after this earliest stage of disease. The opportunity to enjoy life at its fullest with as clear cognition as possible for as long as possible. As others have said, we understand that this particular drug, that has been FDA approved and those that will likely follow in the short term, are not cures. But I think it's important to remember while this is not a debate this morning, I do want to refer back to some of the comments made by a couple of other speakers. This is about the whole class. It's not about one drug. So, criticisms and concerns that people may have about one product should not and must not limit access to future drugs that FDA will review and hopefully approve. And I'm not just speaking about those that may be in Phase III now. This is not a time limited NCD. For the moment, this is open ended.

While that may change, we can't assume that this NCD will be reevaluated in a year or three years or five years. We just don't know that. To cut off access to all future drugs in this class, by declining coverage outright, would be a terrible mistake as a matter of policy. It would be an even worse, and I think unforgivable mistake, in terms of humanity.

We owe it to people that will take Aduhelm and for those that will take the drugs that will follow to study those drugs with real world evidence in as rigorous a way as possible, but they need that access. They deserve that access. And I will just say to the issue that was raised by one of the -- one the earlier speakers about alternatives.

We don't have to treat them as either or. We should be doing absolutely everything we can to advance the public health interventions at the same time that we make available all the FDA approved medications.

Families and individuals and clinicians deserve an opportunity to make their own choices based on the available evidence while we develop more evidence. Families like mine need hearing aids. We need interventions around social engagement. We need interventions like FDA-approved drug therapies.

To the second question, amyloid confirmation is a must. That is at least going to be the case as long as there are questions about the degree of efficacy of amyloid clearance. We now have evidence that amyloid clearance makes a difference. I don't think any of us would say that its conclusive or entirely clear, but we have evidence.

That's true in the Aduhelm trial and it's true in the Phase III trials and Phase II trials for going on with other companies. So, let's get all of that evidence before we make a final decision on that. Let's continue to get amyloid confirmation so we make sure the right patients are the ones giving us real world evidence and are most likely to benefit from these therapies.

As a side issue, I will just say quickly, I know it's not covered by this NCD analysis, but it's incredibly important should CMS approve coverage for this class of medication, that CMS also revisit its earlier CED around head imaging. We need to make sure that there is full coverage for PET and as well as CSF as well as the blood biomarkers and anything else that will help us get the amyloid confirmation that families like mine and millions of others need and deserve to be able to make the right choices about the right medication at the right time.

And then I will just make two quick points about health equity. As you are thinking about health equity, I imagine you are but I will encourage you to be sure to consider both race and ethnicity, but also a range of other forms of health equity, including gender, socioeconomic status, intellectual and developmental disabilities, including Down's Syndrome, rural and other geographically isolated individuals, and issues like neurology deserts, making sure that this drug is available and drugs in its class are available equitably across the country, to all people who qualify in terms of amyloid confirmation and being at the right stage of disease, is incredibly important and that goes to my last point which is I think this must be a national rather than a regional coverage outcome.

We cannot as a matter of policy, as a matter of medical equity, as a matter of social justice, we cannot have parts of the country where individuals are excluded based on where they live. This has to be for everyone in America, regardless of race, ethnicity, geography, gender, socioeconomic status, intellectual capacity, and on down the list.

So, I ask you, and I beg you to make this a national coverage decision approving this class of drugs for all who fit the definition of amyloid confirmation and mild cognitive impairment and early or mild dementia. Thank you.

**Stefanie:** Thank you, Ian. Our next speaker is Susan Bunning from Medical Imaging and Technology Alliance.

**Susan:** Good morning, again my name is Susan Bunning, the Industry Director for Positron Emission Tomography imaging, for the Medical Imaging and Technology Alliance or MITA. I thank CMS for organizing this meeting. With the encouraging FDA approval of Aduhelm, I would like to echo Ian Kremer's comment. In that it becomes more important that the clinically appropriate patients or those who have the amyloid plaque the drug is targeting get identified to go on to treatment. Clinical assessments alone are limited in their ability to accurately diagnose patients, but FDA-approved amyloid and tau imaging PET agents are available today to detect the hallmark pathologies of Alzheimer's disease. MITA believes in order to enhance positive health outcomes from treatment, it's very important to ensure the right patients are placed on the drugs.

Having served as an ad hoc member of the IDEAS study steering committee, considered one of most extensive Alzheimer's disease studies ever conducted, we learned three very important things. In over 11,400 patients, the amyloid PET diagnostic scan changed a patient's disease management over 60% of the time. And in 36% of the cases there was a change in diagnosis, as a result of the PET -- the patient's PET scan results. 77% of patients in this study had a diagnosis of Alzheimer's disease before the PET scan, but in over 3,100 of those scanned, the PET scan was negative, meaning no amyloid pathology could be detected in the brain. But amyloid PET diagnostics are currently not covered by CMS and while much is being debated by CMS and others on how to proceed for the treatment, we urge CMS immediately to open the noncoverage reconsideration request for amyloid PET that was submitted last September to prevent a delay and eliminate the barrier to access to the first ever disease-modifying treatment.

Similarly, we urge CMS to change its policy with regard to Medicare payment. The current inequitable packaged payment methodology presents a second barrier to access, and makes these new targeted diagnosis radio pharmaceuticals a financial liability to hospitals, particularly acute in some states that limit PET scanning outside of hospital



outpatient departments. With regard to equity and inclusion, the follow-up study to IDEASs, New IDEAS focuses on minority populations. A recent GAO report highlighted enrollment challenges as a direct result of impact of CMS packaging payment policy. As an update to the GAO report, only about a handful of the hospitals invited to date have accepted the invitation to participate in New IDEAS. To provide perspective, there were over 125 hospitals that participated in the original study.

We urge CMS to consider the access barriers presented by the current coverage and payment policies for amyloid and tau diagnostic imaging when considering patients selection criteria that will enhance positive health outcomes and equity inclusion. Thank you for allowing me to comment today.

**Stefanie:** Thank you very much Susan. Our next speaker is John Foster, a Biogen trial participant.

**Moderator:** He's not coming up.

**Stefanie:** Thank you. Moving on to Carla Polins from Natural Wellness.

**Moderator:** She's not either.

**Stefanie:** Moving on we have Tajae Platt from Carrington College.

**Moderator:** No, not coming up.

**Stefanie:** Tajae is not coming up either?

**Moderator:** No.

**Stefanie:** Moving on to David Stanke, independent consultant, concerned citizen.

David, you are on if you can just unmute.

**David:** Sorry. I will submit a written testimony later.

**Stefanie:** Great. Thank you very much.

**David:** Thank you.

**Stefanie:** Moving on to Paul Rudolph. Paul you are on. You can go ahead and unmute.

**Paul:** Can you hear me?

**Stefanie:** I can.

**Paul:** I'm Paul Rudolph, I'm a partner at Arnold & Porter. For purposes of this discussion, I'm speaking on behalf of my clients the American Academy of Neurology and American Geriatrics Society and the Society of Nuclear Medicine Molecular Imaging with respect to the joint letter that the three societies submitted earlier this week. The letter was not directly about Aduhelm. They will each be submitting comments on coverage later on. What the letter concerned was the need for CMS to immediately cover PET scans for beta amyloid. We very much appreciate that CMS has proposed to –(audio drop)- for its most non-oncologic through the rulemaking society this year and that's wonderful. Unfortunately, that proposal does not include beta amyloid PET because there's an NCD on beta amyloid PET that limit coverages to certain clinical trials that are approved by CMS.

Paradoxically, if it's finalized, CMS would then be covering tau imaging at the contractor level but would still be noncovering, beta amyloid PET. As everybody knows, beta amyloid PET positivity was required for the participation in the aducanumab trials. We think it's imperative that patients immediately have access to PET scans and we suggest and we agree with what Sue Bunning said but we think there's a better way to immediately let patients have access to beta amyloid PET and that's by using the

rulemaking process to immediately retire the current CED coverage which can be done through publication of the interim final rule with comment on the back end.

Of course, CMS could be free later on to change that, in connection with the coverage of aducanumab, and other monoclonal antibody treatment products, but right now, the only thing that patients have access to for determining whether they have amyloid plaque are CSF tests and while it's true that Biogen is paying for those, and so they are free, it requires a lumbar puncture and there are many, many, elderly people who cannot tolerate a lumbar puncture or many whom a lumbar puncture is not indicated or would potentially be dangerous, even done under ultrasound guidance.

So, there's a huge equity issue right now that Medicare patients don't have access to the one FDA-cleared test that is known to diagnose amyloid plaque and was used in these clinical trials. It is also well-known that many patients don't have amyloid plaque and right now, without making that available, there may be lots of patients without plaque who are going to get aducanumab, and there's no evidence that those patients will benefit. In fact, those patients could be harmed because of the ARIA potential for brain hemorrhages and brain edema.

So, on Monday, we sent a letter to the administrator, Chiquita Brooks-LaSure. We copied Jon Blum, we copied Tamara, Joe Chin and the whole team at CAG on that letter and we would deeply, deeply appreciate it if CMS would strongly consider immediately issuing an interim final rule that would require the CED coverage of the beta amyloid PET and all three societies stand ready to work with CMS to answer questions, to meet with CMS on this extremely important issue for Medicare beneficiaries. Thank you very much.

**Stefanie:** Great. Thank you very much, Paul. Our next speaker is Munir Ghesani from the Society of Nuclear Medicine and Molecular Imaging.

(Silence).

You are on. You just need to unmute.

**Munir:** Now I have the unmute button. Can you hear me well?

**Stefanie:** Yes, we can.

**Munir:** I'm Munir Ghesani, and on behalf of the Society of Nuclear Medicine and Molecular Imaging, thank you for permitting me to provide the comments on the National Coverage Analysis for monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease during the stakeholder call.

According to the Medicare physician fee schedule proposed rule for 2022, and as mentioned by Paul Rudolf earlier, tau PET may soon be covered by CMS, though amyloid PET will not unless CMS takes actions. Both are very important indicators of Alzheimer's disease and coverage will be necessary for both as more monoclonal antibody therapies for the treatment of Alzheimer's disease become approved in the future. Amyloid PET scans were used in Biogen's clinical trials and covered by Medicare through coverage with evidence development to identify suitable patients and to assess their therapy response. Currently, it is the only FDA approved diagnostic to identify amyloid plaque, the substance that aducanumab targets. Other biomarkers such as CSF is currently not approved and as Paul mentioned, the CFS requires a lumbar puncture and though all three biomarkers may be necessary to guarantee patient access, coverage for amyloid PET is of utmost importance. Others were not used to assess patient outcomes in the aducanumab trials. Many elderly patients are not ideal candidates for lumbar puncture due to an anatomic constraint. Amyloid PET scans also provide regional identification of amyloid in the brain, whereas the other biomarkers do not. They simply tell you the presence or the absence whereas the amyloid actually visually provides you distribution to assess in advance.

Additionally, without PET as a gatekeeper, you are potentially giving the drug to patients it was never evaluated in, which could result in toxic side effects and no clear benefit as was mentioned earlier numerous times. Therefore, CMS must eliminate the national noncoverage decision for amyloid PET.

There are actually a couple of studies that have looked at it in details and one randomized trial using 618 patients found immediate notification of beta amyloid PET

findings associated with increased likelihood of changes of diagnostics, disease management, medications, and referral to a specialist at a three month versus delayed notification. Another large trial using more than 16,000 patients before and after study found beta amyloid PET associated with change in management in over 60% of patients with mild cognitive impairment or dementia of uncertain etiology. And change in 36% of patients which is a remarkable number. And so, with all of these studies demonstrating that there's a direct utility of beta amyloid PET, in order to identify the patients more suitable for treatment, it is imperative as I would mention again that the CMS reviews the national noncoverage for amyloid PET. Thank you for the opportunity to speak.

**Stefanie:** Thank you very much. Our next speaker is Dennis Selkoe.

**Dennis:** Yes, this is Dr. Dennis Selkoe. Can you hear me?

**Stefanie:** I can, thank you, go ahead.

**Dennis:** I'm Dennis Selkoe, I'm a neurologist, cognitive neurologist, practicing at Brigham and Women's Hospital and a professor of neurological disease at Harvard Medical School. I cared for hundreds of patients with Alzheimer's disease and have seen the suffering of the patients and their family with this inexorably progressive degenerative disease that is ultimately fatal. Therefore, I favor coverage by CMS of this class of agents that are potentially disease modifying, as everyone on the call knows this is the first time we have had a potentially disease-modifying agent approved and in particular, I think the accelerated approval mechanism that the FDA chose was appropriate for an outcome across both trials about aducanumab of marked amyloid lowering, which is a key biomarker change in Alzheimer's disease.

Indeed, having actually done research on the amyloid and tau alterations in Alzheimer's for the better part of 40 years, I can tell you that amyloid is not only a biomarker, but can be an actual cause of the disease. So, people with rare autosomal

dominant mutations, and APP or pre-symptomatic, unequivocally have Alzheimer's disease caused by amyloid buildup. It's extremely unlikely that sporadic or conventional Alzheimer's disease in late life, which looks very similar to the cases of APP and pre-symptomatic, is unrelated to amyloid itself. The misunderstanding in the field that some individuals can have high amyloid levels but not have cognitive impairment, is just that, a misunderstanding. The point is, that in many chronic diseases, lesions can form before symptoms occur and, in some people, the lesions don't actually cause disease. We all know the example of atherosclerosis, coronary artery disease and stroke can occur in atherosclerosis disease, but there are many patients would die of other reasons and have sometimes severe atherosclerosis in their coronary arteries without ever having an actual angina. Amyloid then is a causative and an early pathogenic feature of Alzheimer's that is followed from everything we know scientifically by enhancement of tau deposition, more neurofibrillary tangles. On this basis, we can say that the four antibodies currently in phase three and in one case, with aducanumab done with phase III, if they remove amyloid and all four have been shown to do that already and in published work, are modifying Alzheimer's disease and therefore, Aduhelm and the three antibodies and the others that follow it are modifying the disease.

I also want to point out that there's the unfortunate use of the term in the lay public of brain swelling, and hemorrhage. ARIA-E is a correct scientific term that was designated long before we knew about Aduhelm and its path to approval and ARIA-E represents a highly focal, sometimes multifocal minor edema in one region of the brain or another. It does not represent general brain swelling.

Similarly, the hemorrhage that we're speaking of are microhemorrhages. They are not the major cerebral hemorrhage that most of us would be concerned about. I had several people in the EMERGE and ENGAGE aducanumab trials including patients who experienced ARIA-E, one knows that because of 25% of patients who get ARIA-E have symptoms whereas 75% in the trials did not have symptoms. The symptoms that occurred included headache, confusion, and some impairment of orientation, the very things we don't want to see but the reality is that many effective medications have side effects and there's extensive information, that the vast majority of patients who are on a drug like

Aduhelm or the others that are following it do not actually get symptoms from ARIA-E or ARIA-A. I should point out that I agree that approval by CMS for coverage for PET scans for amyloid is very important, but I should also say that in the center like ours at Brigham and Women's Hospital and Harvard Medical school, we will recognize on lumbar puncture in those patients in whom it can be done. So, it's very important to say that the earlier trials that targeted amyloid usually did not actually lower the amyloid. They targeted it but they did not have unequivocal evidence.

The four antibodies being considered as a class for CMS coverage, all lowered amyloid plaques dramatically in the brain and that was associated with a variable 20% to 40% slowing of cognitive decline in all four of those. Therefore, I applaud CMS's taking of public comments on this very important disease modifying approach, and I applaud the fact that they are not talking solely by Aduhelm, but about other amyloid antibodies, some of which have even more clear and robust evidence for benefit to patients but have not yet been approved.

Importantly, the notion that amyloid buildup is not directly linked to the cognitive abnormalities of disease, is not scientifically valid, any more than the fact that several peripheral amyloid diseases in other tissues clearly cause organ failure, and the FDA has approved three different agents, three different drugs to lower amyloid in the heart with clear cut benefit. Thank you very much for giving me the time to speak.

**Stefanie:** Great. Thank you very much. Our next speaker is Stephen Salloway from Butler Hospital.

Steven, I see you are on, if you can unmute. I can see you are off mute, but we still can't hear you. Sometimes people double mute.

**Stephen:** Can you hear me?

**Stefanie:** Now we can, go ahead Stephen.

**Stephen:** Terrific, thank you. Thank you for the opportunity to comment today. I'm

Stephen Salloway, professor of the Neurology and Psychiatry at Brown Medical School and Director of aging at Butler Hospital. I devoted my career to treating patients with Alzheimer's disease. I treated 65 patients in the aducanumab in the phase I and phase III for 3-6 years and I was the site PI for others. I'm also an expert in the management of ARIA.

Alzheimer's disease is a progressive terminal illness without meaningful treatments to slow the disease course. It's encouraging that three anti-amyloid monoclonal antibodies have shown substantial amyloid lowering with some evidence of clinical benefit and I support the FDA decision for accelerated approval so that patients who may benefit can have access to the medication while more research is conducted.

More than 200 accelerated approvals of cancer drugs have had a remarkable impact on cancer treatment and we want the same thing for patients with Alzheimer's disease. We have begun treating patients with aducanumab and our protocol closely follows the criteria used in the clinical trials. We treat patients with mild cognitive impairment and mild dementia with elevated amyloid on CFS or PET who have no contraindications such as cerebral hemorrhage. We have more than 100 patients on a waiting list who meet these criteria but the main factor delaying treatment is uncertainty about coverage. We want to ensure all patients can have access, not just those with financial means. Underrepresented populations such as Blacks and Latinos have higher rates of Alzheimer and it's critical that they have access as well. I'm concerned that patients who may benefit will not have access to treatment during the nine months prior to the NCD and may not be eligible for treatment later.

A group of 6 dementia experts has prepared appropriate use recommendations to guide use of aducanumab in clinical practice which should be published very soon, hopefully in the next week or so.

We will also be discussing these guidelines in a section at AAIC, the International Alzheimer's Conference next Tuesday. Treatment with aducanumab will require close partnerships between primary care and specialty providers to help identify patients who may benefit. Treatment will also require access amyloid testing with clinicians knowledgeable in interpretation of these results and training and safety monitoring for



clinicians and radiologists. It's important that CMS also cover the safety monitoring with MRI, which may need to be adjusted a little bit from the FDA guidelines to more approximate what we're seeing in the incidents in the clinical trials.

The medication can be provided in existing infusion centers. The goal of treatment is to preserve independence and quality of life for patients with early Alzheimer's disease. We will need to monitor with the patient and family, measures of cognition, activities of daily living, caregiver burden, and need for additional healthcare services.

Let me give you an example of a patient on long-term aducanumab from our clinic. A 78-year-old retired school principal developed MCI due to Alzheimer's disease. He remained remarkably stable on open treatment with high dose aducanumab for five years, living at home, driving and socializing regularly.

He only began to decline after aducanumab was stopped, and relied more on his family for help. But he's now doing better back on treatment.

Aducanumab is the first drug approved for Alzheimer's in 18 years, and the first to target a key component of the disease. This approval represents a turning point and it's critical that all patients would may benefit have equal access so that we can build on this momentum and advance the treatment of Alzheimer's disease. Thank you.

**Stefanie:** Great. Thank you very much. Our next speaker is Jerry Barocas from Site of Peace. And Stephen, if you can remember to mute, please. Great. Sorry. Stephen, I think one of you is still unmuted. There we go. All right. Jerry Barocas, are you on?

**Moderator:** No Jerry.

**Stefanie:** Okay. Thank you. Moving on, we have Kay Scanlan.

**Moderator:** No Kay.

**Stefanie:** I'm sorry, is she on?

**MODERATOR:** No.

**Stefanie:** Okay. We're going to take just a moment to go back through the list at some of the earlier folks just to make sure that they didn't join later. So if we can recheck to see if

AJ Rice is on.

**Moderator:** No.

**Stefanie:** Robert Kinyua.

**Moderator:** No.

**Stefanie:** Max Linder?

**Moderator:** No.

**Stefanie:** Eilon Caspi.

**Moderator:** No.

**Stefanie:** John Foster.

**Moderator:** No.

**Stefanie:** Carla Polins?

**Moderator:** No.

**Stefanie:** Tajae Platt?

**Moderator:** No.

**Stefanie:** Great. Thank you. Well, thank you everyone, for joining today. We appreciate you taking the time to join our listening session, either as a speaker or just as a participant listening to the comments.

We encourage you, if you haven't made comments or if you want to continue to view other public comments, please visit the web page on your screen.

If there are folks who still want to make comments we are doing another listening session on July 27<sup>th</sup> that registration link was in the press release that went out on this topic and so you can register there if you wish to speak or listen to another session again on July 27<sup>th</sup>. Again, we appreciate all of your comments today and that concludes today's listening session.