

Centers for Medicare & Medicaid Services
Listening Session: National Coverage Determination Analysis
on the Treatment for Alzheimer's Disease
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Ashley Spence: Good afternoon, everyone, and thank you for joining us today. Welcome to this National Coverage Determination Analysis on the treatment for Alzheimer's disease listening session. My name is Ashley Spence and I'm with the Center of Clinical Standards and Quality at CMS and I will moderate the session for you all today. Today I am joined by Tamara Jensen, she's the Director of the Coverage and Analysis Group also at CMS in the Centers for Clinical and Standards, the Clinical Standards, sorry, and Quality. Before we begin, I want to share a few housekeeping tips with you. First, this call is being recorded and we will transcribe this, as it will serve as an official record as a part of the National Coverage Decision and, as you all know, we usually refer to this as NCD. While members of the press are welcome to attend this call today, we do want to note that all press and media inquiries should be submitted via our CMS newsroom media inquiries form, and so you would get to that on the [cms.gov](https://www.cms.gov/newsroom/media-inquiries) website at [/newsroom/media-inquiries](https://www.cms.gov/newsroom/media-inquiries) so again just a reminder for members of the press on that this is where you would submit all your immediate questions.

Today's listening session is another opportunity for CMS to hear public comments as such, we are not gathering written comments or taking questions through the zoom chat function today. We will also not be responding to any comments made or answering questions asked during the comment portion of this call today, so this is, this is a listening session only for CMS. All written comments must be submitted via the NCD tracking document and that link is in front of you on the screen today. The list of today's speakers was compiled based on those who indicated through the registration process that they would like to speak on today's listening session. We will do our absolute best to get to as many speakers as possible, we have a full list and so will, you know, do our best to get through everyone. We do ask that each speaker speak no more than five minutes, so three to five minutes approximately for each person. And we are keeping an eye on time so as we get close to your five-minute mark, we will politely ask the speakers if you could wrap up your remarks to ensure that we can get everyone in. With that we'll go ahead and get started I'll turn the call over to Tamara Jensen and again she's the Director of the Coverage Analysis Group here at CMS. Tamara?

Tamara Syrek Jensen: Thank you Ashley. Good afternoon everyone and again, 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 now refer to 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 future monoclonal antibodies directed against amyloid with an indication for use in treating Alzheimer's 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 NCD remains a CMS cornerstone. CMS follows a long-standing process developed by Congress to determine whether a medical item or service can be covered nationally by Medicare. This includes when an item of 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 develops NCDs using all relevant publish evidence and feedback received from all stakeholders.

The NCD process is open, and it is critical that all stakeholders provide input. We are listening to all feedback received. Through the NCD tracking sheet CMS will continue to provide ongoing communication 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 have been through a thorough evidentiary analysis for Medicare beneficiaries.

The NCD process begins when CMS announces an item or services under consideration by posting a notice, or commonly referred to as a tracking sheet on the CMS coverage website. You can see a link to this tracking sheet displayed on your screen now. CMS posts a specific tracking sheet for each item or service under review. This 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, 2021.

CMS carefully reviews all comments and associated evidence to develop the proposed NCD and decision memorandum. The memorandum contains the analysis of the evidence that supports 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 20, 2022.

Once the proposed NCD is available, the public has another opportunity to provide comments. This is the second 30-day public comment period. To ensure complete transparency, public comments received are posted on the CMS Coverage Group 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 being effective on the same day. Therefore, a final NCD would be completed no later than April 12, 2022.

While the NCD processes are underway, the Medicare contractors representing 12 jurisdictions across the country will make the decision regarding coverage for Aduhelm on a case by case basis, using all available evidence. Please note that Medicare payment rates and codes are developed outside of the NCD process.

As Ashley mentioned today's listening session is an opportunity for CMS to hear public comments. We will not be responding to the comments made or answering questions asked during the comment portion of this call. Again, thank you for participating today, we appreciate your feedback and we look forward to hearing from all of you. Ashley?

Ashley Spence: Thank you Tamara. And now we will go ahead and begin with the actual listening portion of the call. Again, we will call on the individuals that identified themselves as wanting to be a speaker. We will unmute your lines, just a reminder, that you will likely have to unmute yourself on your end if you've muted yourself on your phone and that comments should be held to three to five minutes, so we really want to just encourage folks to kind of stay within those time parameters. With that we will move into our first speaker, and that is Yuval Zabar from Biogen.

Yuval Zabar: Good afternoon, and thank you for the opportunity to offer a brief remark. I'm Yuval Zabar, Medical Director at Biogen and a neurologist. Prior to joining Biogen, I spent 20 years caring for Alzheimer's disease patients. We strongly encourage CMS to cover Aduhelm for the population we studied in our clinical trials, that is patients with early stage AD and confirmed amyloid pathology, so the appropriate patients can receive treatment. Coverage of new innovative therapies is critical. The approval of Aduhelm has already renewed investment activity in Alzheimer's disease research and development. And we're optimistic that other innovative treatments will soon be available for patients. We also recognize the importance of uninterrupted access to Aduhelm. Therefore, we ask the Agency to continue to encourage MACs to cover Aduhelm at the local level, while the NCA process is ongoing. Aduhelm is an amyloid beta directed antibody indicated for the treatment of early Alzheimer's disease. Treatment with Aduhelm should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was studied in the clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease. This indication is approved under accelerated approval, based on reduction in amyloid beta plaques observed in patients treated with Aduhelm. Continued approval for this indication is contingent upon verification of clinical benefit and safety in confirmatory trials. We're working on completing our confirmatory trial in a timely manner.

In the interest of time I'll focus on questions four and five presented in the CMS NCA tracking sheet for monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease. But our formal written response will address all questions contained within the NCA. Patients often discuss their concerns about memory loss and Alzheimer's disease with their primary care physician. Cognitive impairment is commonly detected during primary care visits. In addition to screening for cognitive impairment experienced trained HCPs can initiate a

diagnostic assessment or even a full evaluation. Dementia trained HCPs can detect mild cognitive impairment and early stages of dementia. These HCPs can include primary physicians, family practitioners, internists, nurse practitioners, or physician assistants. Neuropsychologists may provide additional expertise and cognitive assessment. Often patients with cognitive impairment are referred to a dementia specialist, most commonly neurologist geriatricians or geriatric psychiatrist may also function as dementia specialists. Dementia specialists provide greater expertise and diagnosis and treatment options. There will be geographic variability in patient access to experience are trained PCPs and further to specialists, with less access in rural areas. An integrated patient centered team approach to care will optimize diagnosis and care of patients at early stages of disease, including monitoring for ARIA and other safety concerns throughout the course of treatment. A patient centered care team, therefore, should be multi-disciplinary and collaborative among neurologists, geriatricians, geriatric psychiatrists, radiologists, primary physicians, family practitioners and nurse practitioners, or physician assistants, according to available resources and access to care. Patients do require flexibilities because there's a shortage of neurologists and many rural areas lack specialists in particular. Once a patient receives his or her diagnosis, multiple sites of care are available for infusion therapy. Infusions can take place in a variety of settings, including outpatient hospital departments, physician offices, freestanding ambulatory care clinics, independent infusion centers, and potentially in the home setting, which is not currently approved for Aduhelm. Aduhelm is anticipated to be most frequently given at hospital outpatient departments and physician offices. Although integrated delivery networks provide an ideal setting for multi-disciplinary patient centered care, any therapy should not be limited to academic centers. Many underserved and underrepresented patients don't have access to the centers. Limitations of treatment sites could further exacerbate health disparities for patients who are already disproportionately impacted by Alzheimer's disease. The use of virtual technology during the COVID epidemic demonstrated that quality patient care is possible, opening the door to remote collaboration of HCPs and specialists. In closing, Biogen is committed to working with the Agency to support efforts that allow Medicare beneficiaries with early Alzheimer's disease access to amyloid beta directed antibodies. We stand ready to work with CMS, industry, and stakeholder partners to further advance Alzheimer's disease treatments, thank you.

Ashley Spence: Thank you for your feedback. Our next speaker Maha Radhakrishnan, also from Biogen.

Maha Radhakrishnan: Good afternoon, and thank you for the opportunity to address this public forum. My name is Dr. Maha Radhakrishnan and I'm the Chief Medical Officer at Biogen and speak today on behalf of Biogen. Biogen is the manufacturer of Aduhelm, the first FDA approved monoclonal antibody, directed against amyloid for the treatment of Alzheimer's disease. My brief remarks center around the NCA questions on identifying health outcomes that are most meaningful to patients with Alzheimer's disease, and the importance of making diagnosis and treatment opportunities equally available to all Medicare beneficiaries, regardless of gender, race or ethnicity, to ensure health disparities are not worsened in a disease that already

disproportionately impacts minorities and women. Identifying the patient at the right stage to initiate treatment, and doing so early in the disease process, is central to this treatment paradigm. Confirmation of the amyloid plaque deposits and pathology is essential to consideration of a therapy directed at removing amyloid. Generally early accurate detection and treatment is an important step in addressing Alzheimer's disease. There are ongoing challenges in assessing the clinical effects of therapies in that removing amyloid, including slowing progression that have been observed in clinical studies. Among them is a lack of consensus on the definitive and measurable minimally important clinical differences, or MCIDs, in the outcomes of treatment. Part of the measurement challenge is that in the early stage of AD the rate and matter of progression is heterogeneous across patients making MCIDs difficult to pinpoint and apply consistently. As a result, patient experiences and expectations about anti-amyloid therapies will vary and what is important to them will be your personal consideration and appropriate conversations between a patient and physician, and in any patient centered decision making.

Despite these challenges, multiple studies have shown that patients, as well as their caregivers, in the early stage of Alzheimer's, would value any stabilization or slowing of decline with respect to the cognitive function and the ability to perform activities of daily living, maintain social engagement and sustained equanimity in mood and behavior. These patients desperately want to avoid or at least the very least delay becoming a burden to their loved ones. One area in which there is near universal acknowledgement, however, is that the consequences of Alzheimer's fall disproportionately on women, people of color, and individuals with lower levels of education and work. Black and Latino Americans are two and a half times more likely to develop Alzheimer's disease than their non-Hispanic white counterparts. The reasons for this inequity are multifocal but early diagnosis and access to specialized treatment and support services are especially lacking for the Latino American and Black American patients. The delays and diagnosis or missed symptoms may partly be due to the lack of knowledge about the science of normal aging versus early symptoms of possible dementia. But it's also clear, and research has shown, that inadequate access to validated tools for cognitive screening and medical professionals trained in their use, together with any gaps and insurance coverage and racial biases in healthcare, lead to delays or missed opportunities for early detection, intervention and treatment of Alzheimer's disease. Biogen supports efforts by the CMS to consider ways to better understand these inequities and expand access to clinical innovation, including therapies for Alzheimer's for these underserved populations. I thank you for your time.

Ashley Spence: Thank you for your comment. Our next speaker is Brandy Matthews from Eli Lilly.

Dr Brandy Matthews: Hello I'm Brandy Matthews, a behavioral neurologist, presenting remarks on behalf of Eli Lilly and company. We appreciate the opportunity to participate in this stakeholder call on the National Coverage Analysis or NCA for monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease. Eli Lilly is excited that meaningful change for people living with Alzheimer's is upon us. However, hope from the availability of current and future approved amyloid plaque reducing therapies can become reality only if

patients have timely and equitable access to both therapies and diagnostics. The Centers for Medicare and Medicaid Services asks five questions on the tracking sheet for this NCA. We look forward to answering these questions in depth in our written comments. Today we will provide initial thoughts on several questions. At the outset, we wish to note our concern that a class-based coverage determination may be premature at this point due to continuing evolution of this class. Several monoclonal antibodies directed against amyloid plaque are at various stages of development and their therapeutic evidence may become available during or after the completion of this NCA. Each amyloid lowering agent may have different degrees of amyloid plaque reduction, trial entry criteria, dosing approaches, duration of treatment, safety profiles, and clinical benefit.

CMS's coverage policies on Alzheimer's therapeutics should evaluate each product based on its own label, clinical trial design, safety, and results. We urge CMS to ensure that its coverage decision has flexibility that does not limit access to future therapies. Limitations placed on the first Food and Drug Administration approved therapies should not automatically apply to future therapies.

Regarding question two, we believe the enrollment criteria for each therapy's clinical trials can be utilized as a starting point to identify appropriate patients for coverage for a particular therapy post approval. CMS's coverage policy for each drug should mirror those enrollment criteria, such as identification of biomarkers, like presence of amyloid plaque, and Tau staging for use of PET imaging. Existing and emerging diagnostics can identify the patients who likely will and will not benefit from these therapies, as well as informing treatment duration. Existing data suggests approximately 40% of patients clinically diagnosed with Alzheimer's disease are actually negative for amyloid plaque by amyloid PET scan. Amyloid negative patients are highly unlikely to benefit from amyloid plaque targeted therapies, so patient burden from unhelpful therapies would be minimized and economic resources could be saved if these diagnostic tools were readily accessible and reimbursed.

As it relates to question three, when considering issues of equity and inclusion in diagnosis and treatment of Alzheimer's disease, CMS must first recognize and address current inequities in access to diagnostic technologies related to the use of amyloid lowering therapies, including amyloid and Tau PET imaging. CMS's current policies on amyloid and Tau PET, including use of coverage with evidence development for amyloid PET, and not paying separately for these imaging tracers when provided in outpatient hospital settings, significantly limit access to care. We urge CMS to establish appropriate coverage and payment rates for Alzheimer's diagnostics. Second, CMS will need to address potential inequities and access to Alzheimer's therapies. Black and Latinx individuals are disproportionately affected by Alzheimer's and, likewise, are more likely to face obstacles to timely diagnosis, enrollment in clinical trials, and subsequent care. CMS must ensure that coverage policies do not reinforce these obstacles or introduce new barriers.

Questions four and five also raise important considerations for establishing an equitable and inclusive access policy that efficiently meets the needs of patients, while being reflective of clinical trial design and corresponding data. Lilly will provide a deeper perspective within our written comments, but we briefly note here the importance of providing flexibility in both types of healthcare providers included in the patient's treatment teams, such as primary care neurologists and other dimension specialist, as well as the variety of care settings in which therapy may be delivered as potential pathways for establishing equity and inclusion in care. In conclusion, we thank CMS for the opportunity to speak today and we look forward to providing more robust written comments over the coming weeks. We urge providers, payers, and policymakers to work together to provide access to Alzheimer's therapies and diagnostics for patients who are most likely to benefit. Let's together ensure we're helping patients, rather than hindering progress. Thank you.

Ashley Spence: Thank you for your feedback today. Our next speaker is Joanne Pike from the Alzheimer's Association.

Joanne Pike: Good afternoon. I'm Dr. Joanne Pike, Chief Strategy Officer of the Alzheimer's Association. On behalf of all those living with Alzheimer's disease, their caregivers, and their families, thank you for the opportunity to address you today. Our disclosures include the following: the Alzheimer's Association received 0.89% of its total contributed revenue from the biotechnology pharmaceutical diagnostics and clinical research industry, including 0.15% from Biogen and Eisai. This information can be found at [alz.org/transparency](https://www.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 will 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-hour day, seven days a week, 365 day a year helpline and serve hundreds of thousands more providing access and direct support to people living with this disease and their families and communities across America. Through our work, we see firsthand every day the devastating toll Alzheimer's disease takes on individuals, their caregivers, and families. An estimated 6.2 million Americans age 65 and older are living with Alzheimer's dementia and more than 11 million Americans provide unpaid care for them. The trajectory of cognitive and functional decline is currently inevitable. The disease is fatal. For individuals living with Alzheimer's they lose more and more as it progresses. They lose the ability to participate, they lose their independence, they lose themselves. We've heard from countless constituents that in the absence of a cure having more time is a meaningful outcome to individuals with a diagnosis and their families. That is why a National Coverage Determination is so important. It can improve access to a treatment that may provide more time to those with mild cognitive impairment or mild dementia stage of disease. The availability of a therapy is very likely to drive rates of diagnosis beyond the population for whom Aduhelm is indicated. Currently Alzheimer's is grossly under diagnosed. Some estimates indicate that it could be as high as half of all cases remain undiagnosed. And without a diagnosis, individuals cannot plan and make choices about care or participate in

clinical trials benefits beyond the possibility of immediately receiving a therapeutic agent. Individuals for whom the drug is not indicated will nonetheless benefit because they will receive a diagnosis, which also allows for better management of co-occurring chronic conditions.

We encourage CMS and the CAG to consider the impact of the availability of a therapy on caregiver burden as well. Caregivers take on overwhelming tasks in order to support persons with dementia and their daily lives, including bathing and dressing, feeding, keeping them safe, and making every single decision for them all day, every day, and often they do that at great personal expense to their health, economic security, and emotional well-being. In 2020, caregivers of people with Alzheimer's or other dementias provided an estimated 15.3 billion hours of unpaid assistance. Caring for a person with Alzheimer's poses special challenges. Individuals with Alzheimer's require increasing levels of supervision and personal care as the disease progresses. People in the middle to later stages of Alzheimer's experience losses in judgment, orientation, and the ability to understand to communicate effectively. Delaying the decline of individuals with diagnosis can directly and positively impact the health and well-being of their caregivers and care partners, many of whom are also Medicare beneficiaries. As it considers coverage and access, CMS must consider racial and ethnic populations that are disproportionately impacted by Alzheimer's and other dementias and who have been historically underserved in healthcare and underrepresented in research populations. Older blacks are twice as likely to have Alzheimer's or other dimensions as older whites and older Hispanics are about one- and one-half times as likely to have the disease as older whites. We refer CMS and the CAG to our 2021 Special Report "Race, Ethnicity and Alzheimer's in America", a key finding of which is that discrimination remains a barrier to Alzheimer's and dementia care. The Alzheimer's Association is committed to eliminating all barriers to treatment and care and we will support CMS in its own efforts to that end. As new treatments become available, know that the Alzheimer's Association is committed to supporting CMS in making coverage decisions and removing barriers to those treatments for all individuals who could benefit. We are grateful for the Coverage and Analysis Group's careful consideration of all evidence and information. Thank you for the opportunity to comment.

Ashley Spence: Thank you for your feedback today. Our next speaker, George Vrandenburg, from the US against Alzheimer's Association or Organization-sorry about that.

George Vrandenburg: Thank you for allowing me to speak briefly today, my name is George Vrandenburg. I'm the Chairman and co-founder of Us Against Alzheimer's, Chairman of the Davos Alzheimer's Collaborative, and the Chairman of the Global Alzheimer's Platform Foundation which performs clinical trial services. We receive in contributions from thousands of individuals and organizations including a number of sponsors of monoclonal antibodies. Our mission and service to the millions of American families and 10s of millions of American families around the world is to stop Alzheimer's. It is a fatal disease. It robs us of a lifetime of saved memories, it denies us our capacity to enjoy time with our children and grandchildren and friends, it makes us wholly dependent on the very loved ones we've nurtured into independence.

Our work is driven by a sense of urgency to find the means to delay and ultimately prevent those disabling symptoms and humiliating dependence.

This class of monoclonal antibodies are for us a breakthrough disease modifying therapy signaling the promise of slowing our disease and reducing the rate of decline in our clinical progression. What does that mean? More time with friends and family: priceless. As first in class monoclonal antibodies will not be the last in this class and this class of drugs will catalyze the next, much as we've seen in oncology. That will not happen absent the favorable National Coverage Decision and patient access to these promising therapies. We know that these drugs are not a cure, we know that we need to partner with our physicians and researchers to confirm the benefits from these drugs. We want to be partners in finding a solution to this time robbing disease, just as we have invested ourselves in the clinical trials that are bringing these drugs forward. As might be expected, with any new therapy, more needs to be learned about how best to use the therapy, which patients are most likely to respond, which patients are more susceptible to serious side effects, how long to treat, how best to monitor for side effects, and what are the real-world impacts of the therapy on our ability to continue to live our daily family life outside the clinical trial setting. We strongly urge you to provide that favorable National Coverage Decisions for this class of drugs.

Initiating use in the MCI early AD populations in which they were being tested in clinical trials and upon a confirmation of the presence of the amyloid against which these drugs are on. Absent coverage, these drugs will be available only to a small percentage of very high-income Americans. That would be unconscionable. It should be possible to generate useful information about these therapies by systematically collecting data on all patients clinically treated with aducanumab. At the same time, due to the heterogeneity clinicians and patients' decisions regarding the drug, it should also be possible to collect data from similar concurrent patients who are not receiving aducanumab. We believe it vital that the clinical benefit nature's used, and then the future studies be those that matter most to patients. Our own systematic work with Research Triangle International in the What Matters Study, What Matters Most Study, strongly suggest that patients and their caregivers most value the ability to maintain their activities of daily living and their emotional and psychological well-being. Important, importantly, the clinical scales and confirmatory studies should be standardized so that multiple studies produce data that can be compared and contrasted. Future studies should in our view also be designed as other have said to include a more diverse and represented patient population than that, then that that was enrolled in the pivotal phase three trials Aduhelm. We also urge Medicare to consider the substantial benefits of encouraging the clinical use of blood biomarkers as a prescreening mechanism or as an independent confirmation of amyloid pathology. Doing so will speed the diagnostic process, lower diagnostic costs and time, increase access, better engage primary care physicians, and reduce excessive screens from more expensive diagnostic tools. We believe it's important for Medicare to issue a favorable National Coverage Determination that will link payment for aducanumab and other monoclonal antibodies to the generation of evidence that will address critical uncertainties and help inform the patient and clinician decisions. We recognize that there

are many issues and approaches regarding the additional data needed which have yet to be clearly articulated. To help inform CMS and others, and considering the pros and cons of the various approaches, Us Against Alzheimer's and the Duke Margolis Center for Health Policy are convening a working group of experts and other interested stakeholders to develop a framework to guide the development of the data infrastructure and design of clinical studies that will generate the necessary clinical evidence we seek. This working group will explore a range of issues including study design, clinical measures, funding, management, among others. We're planning to make our expert working group output available to CMS and others to serve as a set of proposed specifications and requirements that can be used to evaluate proposals for post-coverage clinical studies for consideration in the context of Medicare coverage. Us Against Alzheimer's is also committed to working with interested experts and stakeholders and CMS to build the required infrastructure and conduct the needed clinical studies. Patients and their families and their physicians care as much as anyone else about the clinical benefit of this class of drugs. Thank you and I appreciate the opportunity to speak today.

Ashley Spence: Thank you for your feedback. Our next speaker, Dean Wong, from Washington University in St Louis's School of Medicine.

Dean Wong: I hope you can all hear me.

Ashley Spence: Yes, loud and clear.

Dean Wong: Thank you. I'm a nuclear medicine physician and a PhD in radiation sciences and currently Professor of Radiology, Neurology, Psychiatry, and Neuroscience at Washington University in St Louis. I'm the immediate past president of the Brain Imaging Council of the Society of Nuclear Medicine and Molecular Imaging. I'm currently speaking as a private citizen and not representing the SNMMI. I do have or concur with the comments of Dr. Ghesani, the President-elect, supporting the need for availability of FDA approved amyloid PET agents to guide antibody therapies. I'd like to elaborate on biomarker use to inform my views on how to proceed. I was, when I was at Johns Hopkins, my lab and collaborators, along with Avid, and now Lily, were fortunate to publish the first human paper on the first FDA approved amyloid grant radio-pharmaceutical florbetapir 45. I should not comment on prior concerns of efficacy of the newly approved anti-amyloid drug but I personally have some concerns. I will restrict my comments to biomarker use by CMS for the newly limited FDA approval for the recent anti-amyloid drug Aduhelm and others to come. I have informally polled many of my colleagues in the field, and I think we generally believe that, as a minimum, all patients being considered for antibody treatments must have an FDA approved biomarker measurement.

Currently amyloid PET would be the most logical choice. The national non-coverage determination CMS has in place for amyloid PET must therefore be reversed to be compatible with this, and this test must be made available to CMS beneficiaries to avoid health inequities. We realize blood and CSF testing for amyloid is evolving, but these tests are not yet FDA approved. Many of us also believe that a subgroup of such patients under anti-amyloid treatment could receive a quantitative baseline amyloid. And a follow up quantitative amyloid PET to be

obtained, following a specified period, such as after year of treatment or after a clinically observed changing cognition is determined by the official treating physician or health care worker. This is an addition, although a subset, in addition to the current qualitative readings that have been approved for three amyloid FA 18 PET tracers by the FDA but not yet by CMS. The advantage of a quantitative change measurement in the subgroup, and I realized that not every center would be able to do this, but a quantitative change measurement in a subgroup would provide further phase 4 evidence for change in cognition related to the reported amyloid reduction of amyloid antibody treatments. This amyloid PET could also be accompanied by quantitative FTP PET before and after one year or suitable clinical observed change in cognition for evidence of neuro degeneration. The use of quantitative PET could be one step beyond the current and original ideas trial and the, and the, soon to, phase 2 ideas sponsored by CMS since quantification would be essential to provide evidence-based change amyloid load with cognitive change in real community situations. I also support the role of Tau imaging, Tau PET imaging by CMS but caution there are several new generation Tau PET tracers and they fall into the more advanced research area, an area that I currently am working in. They would also be an addition, useful addition to amyloid in FTP PET for amyloid treatments which are currently the issue of the CMS discussion now. The Tau PET can be used to accompany cognitive changes correlates are already well established as MTG for neurodegeneration and of course amyloid for anti-amyloid load, but the latter may be somewhat more controversial as we've already discussed. For a lone measurement of cognition. Thank you very much for your time.

Ashley Spence: Thank you for your comment today. Our next speaker, Bob Herman from Axios. And Bob if you are speaking you're still muted. Okay, I think we may have, I saw but I think we may have lost them, we can always circle back in the meantime, we can take the next speaker until Bob reappears and our next speaker is Eric Siemers from Siemers Integration LLC. And we do ask for your patience, for about a minute just to move the speakers around for just a second. Okay again just apologies for the moment of silence as we transition between speakers here. Okay, I think we have our next person I see, so thank you all again for your patience, our next speaker, we have is David Stanke. David your line is unmuted.

David Stanke: Hello, and thank you for the opportunity to speak with you, and about the approval and payment of the drug Aduhelm. I would like to state that Aduhelm is not a cure for Alzheimer's disease. While we've heard a lot of testimony about its how, it's efficacy it does not confident, confidently indicate that it changes the trajectory of cognitive decline. It should not be part of any treatment program for any race, or male or female. My mother had early onset Alzheimer's disease. I know the desire for a cure, and I know that people in this situation will look for anything that has any hope of success. I watched my father help my mother through very difficult years. 40 years ago it was very difficult to get a diagnosis of what was going on, much less a cure. There was no hope for a cure. We adapted and my father specifically adapted to a very painful reality and was able to make life peaceful and secure for my mother, for many years until her death. With information available today, enhancing my father's approach with therapy and support programs will produce a more successful results than administering Aduhelm. My

mother had, when my mother had Alzheimer's, there were many things that would have helped us. Aduhelm was not one of those things. Monthly trips to a medical facility for infusions of 40% chance of Aduhelm causing brain bleed or brain swelling would not have been helpful. Forcing vulnerable family members to lie still for MRIs and PET scans to search the brain for signs of damage would not have been easy. Trying to determine whether swings in cognitive performance were due to the drug or due to the natural progression of the disease would have been stressful. Figuring out how to pay for and deal with uncovered cost of treatment would have been devastating. Perhaps the greatest challenge would have been the dilemma over whether to continue therapy every month when we would be unable to evaluate whether or not it was helping our specific patient. Because the level of change is so small, and so imprecise that a case by case basis will have a very difficult time determining whether the drug is helping. There are levels of coming to terms of the diagnosis of Alzheimer's, the possibility, the cure, is a dream. Gaining years with a loved one who is still able to interact with family to remember friends and to enjoy simple pleasures in life is also a dream.

But the end game is always on the mind in the Alzheimer's family. It's not clear that this drug changes the end game, or even significantly moves the goalposts, not yet. Even if Aduhelm were completely harmless, imperceptibly slowing a disease at high personal and high financial cost of society is a questionable benefit. The expense of Aduhelm is unfathomable considering the potential harm and phantom benefits. This money could be spent on environmental modification and proven therapies that would benefit both patients and their families. As I learned from my father, the greatest peace my mother gained was from being in a family home in a patient and caring environment surrounded by familiar faces. Even when names aren't remembered or weren't remembered she was more relaxed when she was with family in a familiar environment. Making that environment safe is critical, creating an appropriate in-home environment and avoiding institutionalization is more beneficial than administering an ineffective drug. Most homes are poorly equipped for Alzheimer's patients, doors, cabinets, stoves, stairs, bedrooms, bathrooms, all of these things can pose dangers and challenges to patients at different stages of the disease. Relocating a patient to a family home typically requires modifications to accommodate an extra person to make it safer and more comfortable. The \$56,000 per year cost of Aduhelm could cover aid, respite care, relieve family stress, provide therapy and training for caregivers, and a host of devices to enable safer and easier living. It could provide physical, occupational, and cognitive therapies for the patient, including items like hearing aids, items which had been proven to be effective in slowing the progression of the disease. My family was fortunate in circumstances and we managed to be able to house my mother in place and financially pull things together. Most importantly, my father came to terms with the disease and managed the circumstances, he didn't depend on a phantom hope that my mother would recover, he didn't add to her stress with that expectation. He made changes, provided physical and mental stimulation for my mother, he lived with a real hope that he could make her comfortable, keep her safe and find ways to give her peace, despite the progression of a disease that shatters peace and security. We all hope for the cure to this terrible disease, but we need more research on Alzheimer's causes, symptoms, and treatments. We are grateful for those willing to accept the

risk of participating in the trials to forward the development of treatments, but to pay for general mass distribution of a drug that was resoundingly rejected by a panel of medical experts due to insufficient evidence of improvement and abundant evidence of harm is to unleash a promising experiment on an unsuspecting desperate population. The evidence and the weight of scientific evaluation indicate that no one should prescribe, pay for, or use this drug. except as part of clinical trials. Anyone from pharmaceuticals who are selling the drug, including Biogen, from other equipment manufacturers who will gain from the support financial support of this drug cannot be considered unbiased scientists in evaluating whether this drug is effective. Please look at all of the other scientific input and all of the other comments that I've seen in the written testimony and evaluate those who are more likely to be fairly critical of whether this drug is an effective treatment for Alzheimer's. Thank you for your time and I hope you make a very good decision on this.

Ashley Spence: We thank you for your comment today. Our next speaker Claire Levesque from Point32Health.

Claire Levesque: Thank you, my name is Dr. Claire Levesque and I want to thank you for this opportunity to speak in opposition to national coverage for Aduhelm. I appreciate being able to speak after David Stanke because I think he told the story of the difficulties of dealing with Alzheimer's in your family. I'm a board-certified neurologist, for over 30 years I've served as Assistant Professor of Neurology at Boston University, I've treated hundreds of patients with Alzheimer's disease and done research on markers in the brain and the blood of those with Alzheimer's. I'm now Chief Medical Officer of Commercial Products at Point32Health, charged with ensuring quality care for our members over five New England states. But, for me, this is really not an academic exercise. I lost my husband Bill to Alzheimer's disease, just before the pandemic. And because there's a strong family history, I live with the fear that my daughter or my stepchildren could end up with Alzheimer's disease. This is a terrible disease, and I want to find a cure, I want to find a cure from for my family, for the other families and for Point32 Health. But as I look at this, as a doctor, I'm told first do no harm and for me Aduhelm fails this test.

We hear about ARIA amyloid related imaging abnormalities. ARIA-E is edema and has occurred in 35% of those in the clinical trials. ARIA-H is haemosiderin deposition which is bleeding into the brain. I want to be clear that the brain is a very complex organ and even very small areas of bleeding or swelling in parts of the brain can lead to real declines in function for people. If this happens in a part of the brain that affects your ability to speak, you lose some ability to communicate with your family. It could impact you in areas that impair sensation or muscle strength or perceiving vision, all of these things again cause these disabilities. We don't have enough information from Biogen about what happened to these individuals with these side effects, but I can say that in the early stages of Alzheimer's families really want their loved ones to be at the highest possible level of function, so even a temporary increase in disability would be very, very disturbing to both the patient and the family and better understanding of what these side effects are is critically important. We also don't know how long these persisted and whether

these were temporary, which again is a critical thing for helping people understand whether this treatment is really offering any sense of hope, or just really offering risks of side effects. Adding to that my concern about missing data, we heard Biogen offering a commitment to making sure that this drug was available to people across multiple populations. But there's a very big problem with this, because nonwhites were very small number in the studies that they performed. And we know Alzheimer's disease does not discriminate, people of all races and ethnicities get Alzheimer's disease. And I question how neurologists will face this when they have a person of color in front of them, and they have to actually say to that person "I don't know if this drug works for you, because your population was not studied, I don't know what dose is should be given and I don't know if it's safe". So, I worry about that and I worry about people of color who are facing the difficulties of Alzheimer's disease. I've been asked by folks what I would do if Bill was still here with me and I have to say that I would not want him to take this drug. I feel like it has unproven benefit, and it has high risk, and it would have felt terrible if I started him on this drug when he was in the early stages of the disease, and he had any level of decline, because that would have robbed both of us have precious moments together. So, in closing, I want a cure for Alzheimer's. I want to cure for my daughter, for my stepchildren, I want to cure for all of the families who are dealing with this now or and who will deal with this in the future, I want to cure for Point32Health but I'm still very concerned that Aduhelm isn't unproven benefit and high risk. I respectfully advise the CMS to view this as investigational and experimental and not to provide unilateral coverage for Aduhelm at this time. Thank you for listening to me.

Ashley Spence: We thank you for your feedback. Our next, our next speaker today is Margaret Rhondeau, excuse me, from the National Down Syndrome Society.

Margot Rhondeau: Hi, can you hear me?

Ashley Spence: Yes, loud and clear.

Margot Rhondeau: Hi, thank you, good afternoon, my name is Margaret Rhondeau. I am the Senior Director of Health and Wellness at the National Down Syndrome Society. On behalf of NDSS I'm honored to speak to you today, and thank you for this opportunity. Individuals with down syndrome face a much higher risk of Alzheimer's disease in the general population. They are diagnosed at a younger age and the degrees, sorry, disease progression is more rapid. Alzheimer's disease is now the leading cause of death for individuals with down syndrome. Individuals with down syndrome and their families need Medicare and commercial payers to cover and care for those with down syndrome and Alzheimer's. Specifically, we asked that the following three elements we considered. One, individuals with down syndrome should never be excluded from coverage of new therapies or benefits under the Medicare program or commercial plan. Denial of coverage for an underlying health condition is prohibited under most types of coverage, including employees sponsored coverage and Medicare. Two, physicians should be given the professional latitude to make an individualized assessment and diagnosis as well as development of a treatment plan. Physicians with patients with down syndrome should be authorized to use appropriate biomarker and other diagnostic protocols as a basis for determining

eligibility for any medication authorized for use to mitigate the effects of Alzheimer's disease and these physicians should be permitted to use his or her judgment when determining whether a patient has an amyloid plaque accumulation and is living with Alzheimer's disease. Likewise, the physician should have the professional autonomy to make a shared decision with the individual with down syndrome and his or her family as to whether the benefits of the treatment outweigh the risk for the individual with down syndrome. This is particularly critical for the down syndrome population, which tends to be more susceptible to drug related adverse events such as micro hemorrhages. In addition, physicians should have the ability to order additional imaging test to monitor individuals with down syndrome receiving treatment to ensure that they are not experiencing life threatening side effects. Three, payment for this treatment must be reasonable. Many adults with down syndrome cannot afford a co-payment or their secondary coverage, such as Medicaid, will not pay. Inability to pay should not be fatal. We asked as CMS begins the careful review to determine the efficacy of a national Medicare coverage policy for monoclonal antibodies that target amyloid for the treatment of Alzheimer's disease, that they're equitable and cognizant to these special circumstances are adults with atypical life situations. We encourage CMS not to create additional barriers restricting coverage, there by restricting fundamental care for people with down syndrome and other intellectual disabilities. Individuals with down syndrome need to be a part of the discussion with a seat at the table. Thank you very much.

Ashley Spence: Thank you for your feedback today. We've had several members identify or several participants today identify as speakers, and we are going through the list again so we just asked for your patience towards the end of this call, as we began to look through our list again to ensure that we've, that we've basically elevated all of the people that need to speak, that asked to speak, to the speaker line so if you just give us a couple seconds. Okay, so we have our next speaker on the line, so we have John Dwyer from the Global Alzheimer's Platform. Your line is unmuted.

John Dwyer: Thank you and thank you for allowing me to participate. My name is John Dwyer, I am the President of the GAP foundation and co-founder of Us Against Alzheimer's. My family history is relevant to this discussion to the extent that my grandmother and eight of my father's siblings including himself all died of Alzheimer's, happily my generation is less, less diseased today, hit by the disease, but I would say in tracking the 10 individuals in my large Irish catholic family, we are finding that about three out of ten so far have been mis-diagnosed. With that, as way a background, the Global Alzheimer's Platform Foundation is a patients, patient-centric enterprise designed to reduce the cost and lessen the duration and, most importantly, improve the quality of Alzheimer's clinical trials. We have concluded four therapeutic studies and are in the active process of conducting another seven all in combination with major clinical trials sponsors, some of whom have testified here. And so obviously when it comes to transparency, our enterprise is uniquely active in providing services and consulting work to clinical trial pharma sponsors and therefore our revenues highly weighted towards those sponsors. That said, our foundation is a not for profit dedicated to the benefit of patients and no one else in the first

instance. What we would ask the CMS team to think of now is your, we're going to hear a lot over the course of this NCD process about the underlying merits of the Aduhelm drug. We firmly believe that whatever CMS does needs to be done in a manner that anticipates the rich march of the science, there are many molecules making its way through clinical trials, obviously Aduhelm is one that we have historically supported and not to be ambiguous, we support a positive coverage determination by CMS, but the structure of your determination and how you arrive at it is at least as important as the positive determination itself. In that regard, we will obviously provide more written remarks, but we think that the one of the unique elements of trying to conduct studies, and for you to make a meaningful determination, is to recognize the unique risk of variability in how we measure the presence of Alzheimer's pathology. We strongly advocate for CMS to take a holistic approach as it considers how it will arrive at its decision and how it will reimburse the system for clinical practice to evaluate and allow patients to go on Aduhelm or any other monoclonal antibody, in particular, there are a whole host of technologies that are 5-10-K cleared by the FDA and that are reimbursable under current CMS reimbursement and blood plasma tests that are laboratory tests that are, in fact, in our opinion in uniquely qualified to contribute to clinical practice in making informed decisions about whether patients are significantly at risk for Alzheimer's and these technologies should be deployed rigorously and routinely in clinical practice prior to advancing to a PET image. It will help families get a better handle on the information relevant to a patient's condition, help physicians to make an informed decision, and overall diagnosis avoid patient, unnecessary patient cost, and system cost for going to more expensive modalities, such as PET images which we very much acknowledge the importance of when appropriately applied to informing whether Aduhelm should in fact be administered. In addition, this discussion around rigorous infrastructure will substantially help CMS generate data that will inform its decision, using much more objective, less variable data on the presence of pathology and clinical cognitive scales that will inform you on the effectiveness and its unique contribution to the patient journey. In that regard, we are strongly encouraging CMS to consider these processes as it figures out its determination, because if we take learnings from what we're seeing in clinical trials and from your own IDEAS study, it has subsequently been learnings from those that have moved us towards centralized readers for clerical PET images, so that the variability between clerical imaging centers is mitigated and the use of digital tests that have a more objective baseline so that CMS can look at that data and see changes in cognitive level, in addition to the informed impressions of physicians.

Finally, and I think this is a point that we feel is often overlooked, the use of a holistic approach like this will greatly improve the issues that have been raised by others with respect to the inclusion of underrepresented populations and trials. This is nothing unusual, I regret to say, and I think everybody on this call knows, that all clinical trials in general struggled to get adequate representation of African Americans, Latino-X, Asian Americans, and Native Americans. Part of the reason for that is trust, but another part of it is access to the technologies and centers that can allow them to be included in these kind of measurement processes and best practices for clinical practice. If we are routinely and rigorously calling upon the use of more objective measures in the forms of digital cognitive tests and blood plasma tests technologies that are easier to deploy

in centers that serve low income populations of every race and ethnicity, the likelihood of being able to better involve them in this determination process and in trials and practice more broadly in our experience is much improved. We have a trial underway called Bio-Hermes, a rather unique AD biomarker platform study. Our goal in that study is 20% participation among its thousand participants will be people of underrepresented populations and we were, just in the early days, because it's not completed, tell you that we are very successful in recruiting from those populations in the manner I have described. We will provide more detailed remarks in writing. We thank you for your time, we know this is a difficult process, critically important all of the patients that currently have no approved therapy for their condition. And that cannot be emphasized enough. And with a strong approach reimbursed appropriately by Medicare, we think that the field, the neurology field and primary care physicians, can indeed use Aduhelm in a manner that will advance the care of patients that can benefit from it. Thank you very much.

Ashley Spence: Thank you for your feedback. Our next speaker, David Rind from the Institute for Clinical and Economic Review.

David Rind: Thank you, and are you able to hear me?

Ashley Spence: We are.

David Rind: Great, thank you. Good afternoon, and thank you for providing me this opportunity to make a public comment. I'm David Rind. I'm a primary care physician in Boston and like nearly everyone making comments I have experienced the devastation of Alzheimer's dementia firsthand in friends, colleagues, and family. I'm also the Chief Medical Officer of ICER, the Institute for Clinical and Economic Review. ICER is an independent nonprofit that looks at the comparative effectiveness and cost effectiveness of new therapies and treatments. Last September ICER began a 10-month public process of reviewing aducanumab. As part of that process we engaged stakeholders, including patients, families, patient groups, and clinicians. We also engaged with the manufacturer and had multiple contacts and discussions with them over the period of the review. ICER, in consultation with outside experts, carefully reviewed the information on aducanumab, including the data from the phase one B trial and the randomized trials ENGAGE and EMERGE. We also review the explanations and analyses put forward by the manufacturer to explain why the ENGAGE trials had not found a benefit. Aducanumab clearly reduces beta amyloid in the brain and does so when it does in dependent fashion. In both ENGAGE and EMERGE, patients treated with high dosage aducanumab had greater reductions in amyloid than those treated with low dose aducanumab. And those treated with low dose aducanumab have reductions in amyloid compared with placebo. However, prior trials have failed to demonstrate that reducing brain amyloid in patients with Alzheimer's disease improves clinical outcomes. As such, rather than trying to discover why ENGAGE was negative, the question that should have been asked was why the trials came to conflicting results. ICER concluded that the dose exposure explanation, put forward by the manufacturer, was unlikely to be correct. While this specific post hoc analysis of ENGAGE does lead to results that appear to make sense, if the same criteria are applied to the positive trial EMERGE, you find that there is

no similar connection between received dose and outcomes. As such, it seems more likely that the post PV4 analysis of ENGAGE is simply a post hoc analysis that happened to find a positive result by the combination of chance and multiple testing. We do not know why EMERGE and ENGAGE had different results, but even in EMERGE, the results at 26 and 50 weeks show numerically larger improvements in CDRSB with low dose treatment than high dose treatment. The results at week 78 with high dose treatment may be due to chance. And that there were two opportunities for a positive result, one before the trial was stopped for futility, and another one additional data were gathered and EMERGE was realized.

When ICER presented our results to an independent panel on July 15, the panel voted 15 to zero that the evidence was not adequate to demonstrate that aducanumab provides a greater net health benefits and supportive care alone. Clinical experts at our meeting and many others, feel that the current evidence base inadequate to demonstrate that aducanumab works at all, or that if it does work that its benefits exceed its known harms. We believe it is a disservice to patients to administer aducanumab without demonstrating benefit and that the best option would be a third randomized controlled clinical trial prior to coverage. The ICER report make specific suggestions on modifications to the trial design used in EMERGE and ENGAGE to reduce the risk of functional blinding by ARIA. If CMS decides instead on a path of coverage with evidence development, it is important to recognize that the efficacy of aducanumab will not be answerable with observational and or registry data. Where two randomized trials left this question unanswered, observational data will not fill that gap. If the CDE path has taken, we recommend that CMS work with the National Institutes of Health or the Medicare evidence development and coverage advisory committee to develop an evidence development research design that is rigorous feasible and timely. ICER's report and recording of our July 15 meeting are publicly available at icer.org. Thank you.

Ashley Spence: Thank you for your feedback. Our next speaker today is Marc Archambault. Marc, your line is unmuted.

Marc Archambault: Hello, thank you for letting me talk here for a few minutes. I'm just going to tell you a little bit of how things went for me. I went to a hospital in Rhode Island, in Providence, to do studies for everybody, for myself, my children. So, like helpful, that was in late 2013, hoping that I was not, I don't, I wasn't going to have it. During many years I did four studies, I was happy to do that, my dad passed with Alzheimer's at the age of eighty-eight and the symptoms started when he was eighty. I did get a diagnosis late in '14 and I was 62 at the time, or sixty-seven now. Dr Salloway and the people who works with the wonderful work.

And because people know I have Alzheimer's they often will stop me on the road or on the store and worry about a problem for themselves or for families or friends and I just say go to Butler hospital. I decided that I would not hide having Alzheimer's and I started to walk, talk to people who ever wanted to talk with me in 2017, I just tell my story. I, there's a lot of things that I like to tell people who know nothing about Alzheimer's, but what I always spoke about was if anybody that was in the room and if they have friends or family with Alzheimer's, I would ask

them how many people, how many people have that. Sometimes 50%, sometimes with 80%, that they know and then I would ask do you still see them, especially on the friendship side. And a lot of people said no, and I was able to say, because it's a little scary, I said just tell them yourself sorry that you're going through that and stay friendly with them for the patient, but also for the caregiver that's a tough, tough job. Let's see, I hope, I hope that people who have Alzheimer's will have access to the new drug. For all and not just for the wealthy. I was the first person that got this product last month on the 16th.

And I was happy to do it. I believe it will work, knowing that maybe it won't be as good as I thought or other kinds of things I guess. But I'm proud that I did it and I hope that it'll do what we hope for. I've had two infusions since, just two. And I had no problem in many ways, because of having those I just thought I would say that, and I think people who have Alzheimer's and their families deserve a shot of this drug. Thank you.

Ashley Spence: Thank you for your feedback today, and thank you all for joining us today, this concludes our list of speakers. As a reminder, as we said at the top of the call, this call will be transcribed to serve as an official record as a part of the NCD process. However, all written comments, as you know, must be submitted to the NCD tracking document and again the link is before you on the screen. Again, we thank you for your time today and this concludes our session. Have a great day.