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BY ELECTRONIC DELIVERY (http://www.cms.gov)

Tamara Syrek-Jensen
Director, Coverage and Analysis Group
Centers for Medicare & Medicaid Services
7500 Security Blvd.
Baltimore, MD 21244

RE: Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease (CAG-00431R)

Dear Ms. Syrek-Jensen:

Eli Lilly and Company (Lilly) appreciates the opportunity to comment on the proposed reconsideration of the coverage decision for Beta Amyloid Positron Emission Tomography (PET) in Dementia and Neurodegenerative Disease.[1] Lilly has been committed to Alzheimer's research for more than 30 years and remains determined to find solutions for this unrelenting and fatal disease. Our company has advanced the science of Alzheimer's Disease (AD) diagnosis and treatment by discovering and commercializing imaging agents, including Amyvid (florbetapir F18) and Tauvid (flortaucipir F18), both F18 PET agents capable of discerning the presence of amyloid plaques and tau, respectively, in the brain. We have supported multiple studies within CMS's Beta Amyloid (Aβ) PET Coverage with Evidence Development (CED) program as well as countless studies beyond the CED program which have contributed to critical advancements in Alzheimer's patient care.

We believe we are on the brink of meaningful change for people living with AD. However, the potential benefits of amyloid plaque targeting monoclonal antibodies may only be realized when patients have timely and equitable access to both diagnostics and therapeutics. Therefore, **Lilly supports reconsideration of the Aβ PET NCD and rescission of the one-scan per lifetime Medicare coverage limit. We also strongly urge CMS to clarify that Aβ PET is reasonable and necessary and therefore to stop forcing Medicare beneficiaries into clinical trials as a condition for them to obtain coverage for Aβ PET scans. Accordingly, CMS should clarify that coverage will no longer be limited to "coverage with evidence development" efforts.**

I. Reconsideration of the Amyloid PET NCD Is Timely and Appropriate

Lilly applauds CMS for recognizing it is time to reconsider the Aβ PET coverage decision, which is nearly a decade old and which has not kept pace with clinical developments in AD treatment.

[1] CMS, National Coverage Analysis (NCA), Tracking Sheet: Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease. (Published June 15, 2022). Available at https://www.cms.gov/medicare-coverage-database/view/ncacal-tracking-sheet.aspx?ncaid=308.

Specifically, on June 7, 2021, the FDA approved Aduhelm® (aducanumab-avwa) to treat AD in patients with mild cognitive impairment or mild dementia.[2] On July 6, 2022, the FDA filed a biologics licensing application (BLA) for lecanemab, an investigational humanized monoclonal antibody (mAB) for AD treatment.[3] And Lilly expects the FDA will shortly file a BLA for donanemab, Lilly's own investigational humanized mAB for AD treatment. Lecanemab has been granted priority review by FDA and donanemab may also be granted priority status, leading to the approvals, if granted, likely issued in early 2023. Within its recent NCD for monoclonal antibodies directed against amyloid for the treatment of AD, CMS itself declared, "donanemab is promising." The emergence of treatment options for AD that are reliant on confirmatory Aβ PET scans belies CMS's stated rationale for placing limitations on coverage of Aβ PET, namely that Aβ PET scan results "would not change clinical management."[4] Because AD therapies are now a reality – and because identification of appropriate patients for monitoring those on potential therapies is based, in material part, on Aβ PET scans – clinical management of Medicare beneficiaries will (and should) change depending on Aβ PET results. In light of this fact, it is high time CMS revised the Aβ PET NCD.

II. Ongoing Evidence Development Requirements for Beta Amyloid PET Are Unreasonable and Unnecessary

While the opening of the reconsideration is timely, it will only be meaningful if CMS is comprehensive in their reassessment of the NCD. CMS's notification announcing reconsideration of the Aβ PET NCD lacks the necessary comprehensiveness. CMS states only that it is considering elimination of the one-scan per lifetime limit but is unclear if such scans would still only be covered in the context of further evidence development studies. **Lilly urges CMS to update the Tracking Sheet to notify stakeholders that CED will also be reassessed.**[5] CMS should acknowledge that the clinical evidence is clear and well-developed: Aβ PET scans have empirically and repeatedly, even in the absence of disease-modifying therapeutics, demonstrated significant clinical utility by causing changed clinical management, changed patient diagnoses, and improved provider confidence. Accordingly, **CMS should remove its requirement to develop any additional evidence as a coverage criterion**. The data within the CMS approved CED trials and outside of those trials, across the Medicare patient population, in other countries, in clinical settings, and in non-clinical settings is simply too overwhelming to ignore. We have identified more than 30 relevant studies and summarized the relevant findings below:

1. *Association of Amyloid Positron Emission Tomography With Subsequent Change in Clinical Management Among Medicare Beneficiaries With Mild Cognitive Impairment or Dementia*. The evidence development framework endorsed by CMS resulted in the Imaging Dementia –

[2] Biogen, *FDA Grants Accelerated Approval for ADUHELM™ as the First and Only Alzheimer's Disease Treatment to Address a Defining Pathology of the Disease*, [Press Release].
[3] Biogen, *The U.S. FDA Accepts and Grants Priority Review for EISAI's Biologics License Application of Lecanemab for Early Alzheimer's Disease Under the Accelerated Approval Pathway.* [Press Release].
[4] CMS, *Medicare Program; Reconciling National Coverage Determinations on Positron Emission Tomography (PET) Neuroimaging for Dementia*. 83 Fed. Reg. 15572-15577 (April 11, 2018).
[5] Lilly continues to maintain that CMS lacks the statutory authority to impose CED requirements in the manner set forth by the AB PET NCD. We encourage CMS to review the Supreme Court's recent holding in *West Virginia v. Environmental Protection Agency*, __ U.S. __ (2022), which requires agencies asserting claims of broad regulatory power with great "economic and political significance" to point to "clear congressional authorization" to regulate in that manner. We also direct CMS to, and incorporate by reference, Lilly's position at pages 5 through 7 of its February 10, 2022 letter commenting on the National Coverage Analysis (NCA) for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (CAG-00460N). We do not believe the Final Decision Memo supporting that NCA cured any of the deficiencies identified by Lilly.

Evidence for Amyloid Scanning (IDEAS) Study and subsequent New IDEAS Study. The IDEAS study included 11,409 participants initially characterized as having mild cognitive impairment (MCI) or dementia of uncertain cause. **Ninety days after Aβ PET, patient care plans changed (compared with the pre-PET plan) in 60.2% of patients initially characterized as having MCI and 63.5% of patients initially characterized as having dementia of unknown cause. Hence, Aβ PET was associated with substantial subsequent changes in the management of diagnostically challenging patient cognitive disorders.** Rabinovici GD, Gatsonis C, Apgar C, et al. JAMA 2019;321:1286-94.

2. *Critical Review of the Appropriate Use Criteria for Amyloid Imaging: Effect on Diagnosis and Patient Care*. "**In conclusion, our case series suggests that amyloid imaging information frequently results in both diagnostic and treatment plan changes**. At least in the hands of the dementia experts who took part in this study, it seems that the benefit for the early-onset group lies in confirming the presence of cortical amyloid consistent with a diagnosis of AD, which prompted the referral for the amyloid PET scan in the first place, whereas the benefit for the late-onset group lies in identifying amyloid-negative cases. **In both groups, physicians made therapeutic changes in over two-thirds of the cases**." Apostolova LG, Haider JM, Goukasian N, et al. Alzheimers Dement (Amst). 2016;5:15-22. Published 2016 Dec 18. doi:10.10H2:H4616/j.dadm.2016.12.001.

3. *Clinical Utility of Amyloid PET Imaging in the Differential Diagnosis of Atypical Dementias and Its Impact on Caregivers*. "**Amyloid PET resulted in a diagnostic change in 9/28 cases (32.1%)**. There was a 44% increase in diagnostic confidence. **Altered management occurred in 71.4% (20/28) of cases**. Knowledge of amyloid status improved caregivers' outcomes in all domains (anxiety, depression, disease perception, future anticipation, and quality of life)." Bensaïdane MR, Beauregard JM, Poulin S, et al. J Alzheimers Dis. 2016;52(4):1251-1262. doi:10.3233/JAD-151180.

4. *Assessment of the Incremental Diagnostic Value of Florbetapir F 18 Imaging in Patients With Cognitive Impairment: The Incremental Diagnostic Value of Amyloid PET With [18F]-Florbetapir (INDIA-FBP) Study*. Concluding that "Amyloid PET in addition to routine assessment in patients with cognitive impairment has a significant effect on diagnosis, diagnostic confidence, and drug treatment" and **finding that care plans (as defined by drug initiation or discontinuation) changed in 65.6% patients with positive scan results who had not previously received those drugs, and the use of the drugs was discontinued in 33.3% patients with negative scan results who were receiving those drugs** ($P < .001$). Boccardi M, Altomare D, Ferrari C, et al. JAMA Neurol. 2016;73(12):1417-1424. doi:10.1001/jamaneurol.2016.375.

5. *Additive Value of Amyloid-PET in Routine Cases of Clinical Dementia Work-Up After FDG-PET*. A study comparing diagnosis and care management between FDG PET and Aβ PET observed that **when Aβ PET was used, the "most likely prior diagnosis was changed in 28% of cases**. The highest impact was observed for distinguishing Alzheimer's dementia (AD) from fronto-temporal dementia (FTLD), where [AB] PET altered the most likely diagnosis in 41% of cases." The authors concluded the "differentiation between AD and Frontal Temporal Lobe Dementia was particularly facilitated by amyloid-PET, **predicting a considerable impact on patient management**, especially in the light of upcoming disease-modifying therapies." Brendel M, Schnabel J, Schönecker S, et al. Eur J Nucl Med Mol Imaging. 2017;44(13):2239-2248. doi:10.1007/s00259-017-3832-z.

6. *Clinical Utility of Amyloid PET imaging with (18)F-florbetapir: A Retrospective Study of 100 Patients*. A retrospective review of the first 100 patients who had amyloid PET imaging as part of clinical practice in a memory center in the United Kingdom. "Amyloid PET was primarily used to investigate patients with atypical clinical features (56 cases) or those that were young at onset (42 cases)." Amyloid PET "results could not reliably be predicted by pre-imaging investigations" including MRI and CSF. **Amyloid PET "led to a change in diagnosis in 30 individuals" and "a change in management in 42 cases"** most commonly, "the addition of memantine or an acetyl cholinesterase inhibitor (24 patients)." Carswell CJ, Win Z, Muckle K, et al. J Neurol Neurosurg Psychiatry. 2018;89(3):294-299. doi:10.1136/jnnp-2017-316194.

7. *Added Value of 18F-florbetaben Amyloid PET in the Diagnostic Workup of Most Complex Patients with Dementia in France: A Naturalistic Study*. "**PET results led to changed diagnosis and improved confidence in 66.8% and 81.5% of patients, respectively, and altered management in 80.0% of cases**." Ceccaldi M, Jonveaux T, Verger A, et al. Alzheimers Dement. 2018;14(3):293-305. doi:10.1016/j.jalz.2017.09.009.

8. *Atrophy, Hypometabolism and Clinical Trajectories in Patients with Amyloid-Negative Alzheimer's Disease.* "**After the amyloid scan, clinicians altered the diagnosis in 68% of amyloid-negative patients** including 48% of amnestic versus 94% of non-amnestic and non-specific cases." Chételat G, Ossenkoppele R, Villemagne VL, et al. Brain. 2016;139(Pt 9):2528-2539. doi:10.1093/brain/aww159.

9. *Association of Amyloid Positron Emission Tomography with Changes in Diagnosis and Patient Treatment in an Unselected Memory Clinic Cohort: The ABIDE Project*. Observing that "**the suspected etiology changed for 125 patients (25%) after undergoing amyloid PET**" and that "**in 123 patients (24%), there was a change in patient treatment post-PET**, mostly related to additional investigations and therapy."de Wilde A, van der Flier WM, Pelkmans W, et al. JAMA Neurol. 2018;75(9):1062-1070. doi:10.1001/jamaneurol.2018.1346.

10. *Re-Evaluation of Clinical Dementia Diagnoses with Pittsburgh Compound B Positron Emission Tomography*. Observing in a small study that between FDG PET and a follow-up Aβ PET scan, "**the initial clinical diagnoses were changed in one third of the patients** (6 out of 18) during follow-up." Degerman Gunnarsson M, Lindau M, Santillo AF, et al.. Dement Geriatr Cogn Dis Extra. 2013;3(1):472-481.

11. *Added Diagnostic Value of (11)C-PiB-PET in Memory Clinic Patients with Uncertain Diagnosis*. "A total of 57 patients (17 females, 30 males; age 65.7 years, range 44.2–82.6) were included in the study. Twenty-seven had a positive PiB-PET scan. At the first diagnostic evaluation, 16 patients were given a clinical Alzheimer's disease diagnosis (14 PiB positive). **Of the 57 patients, 13 (23%) were diagnostically reclassified after PiB-PET ratings were disclosed. The clinicians' overall confidence in their diagnosis increased in 28 (49%) patients.**" Frederiksen KS, Hasselbalch SG, Hejl AM, Law I, Højgaard L, Waldemar G. Dement Geriatr Cogn Dis Extra. 2012;2(1):610-621. doi:10.1159/000345783.

12. *Potential Impact of Amyloid Imaging on Diagnosis and Intended Management in Patients with Progressive Cognitive Decline*. "A total of 229 patients participated in the trial (113 amyloid positive, 116 amyloid negative). "**After receiving the results of the florbetapir scan,**

diagnosis changed in 125/229, or 54.6% (95% confidence intervals (CI), 48.1%-60.9%), of cases, and diagnostic confidence increased by an average of 21.6% (95% CI, 18.3%-24.8%). **A total of 199/229 or 86.9% (95% CI, 81.9%-90.7%) of cases had at least 1 change in their management plan**." Grundman M, Pontecorvo MJ, Salloway SP, et al. Alzheimer Dis Assoc Disord. 2013;27(1):4-15. doi:10.1097/WAD.0b013e318279d02a.

13. *Initial Physician Experience with [18F]Flutemetamol Amyloid PET Imaging Following Availability for Routine Clinical Use in Japan.* "As part of a Japanese post-approval study to measure the safety of [18F]flutemetamol PET, the association of amyloid PET results with changes in diagnosis and diagnostic confidence was assessed." "**Amyloid PET imaging led to change in diagnosis in 15/44 clinical subjects (34%). Mean diagnostic confidence increased by approximately 20%, from 73% pre-scan to 93% post-scan.**" Hattori N, et al. J Alzheimers Dis Rep. 2020.

14. *Amyloid Imaging for Differential Diagnosis of Dementia: Incremental Value Compared to Clinical Diagnosis and [18F]FDG PET.* "**After disclosure of the amyloid PET results, clinical and [18F]FDG PET diagnoses changed in 23% and 18% of patients**, respectively, and agreement between both ratings increased from 62% to 86% ($p < 0.001$). **The accuracy of clinical and [18F]FDG PET diagnoses improved from 71% to 89% ($p < 0.01$) and from 76% to 94% ($p < 0.001$)**, respectively." Hellwig S, Frings L, Bormann T, Vach W, Buchert R, Meyer PT. Eur J Nucl Med Mol Imaging. 2019;46(2):312-323. doi:10.1007/s00259-018-4111-3.

15. *Utility of Amyloid and FDG-PET in Clinical Practice: Differences Between Secondary and Tertiary Care Memory Units.* In a study comparing FDG PET and Aβ PET diagnoses, researchers observed that "**the primary diagnosis changed after [AB] PET in 17.2% of cases.**" Lage C, Suarez AG, Pozueta A, et al. J Alzheimers Dis. 2018;63(3):1025-1033. doi:10.3233/JAD-170985.

16. *Clinical Impact of [18F]flutemetamol PET Among Memory Clinic Patients with an Unclear Diagnosis*. "**[AB] PET led, overall, to a change in diagnosis in 92 of the 207 patients (44%)**. A high percentage of patients with a change in diagnosis was observed in the MCI group (n = 67, 51%) and in the dementia NOS group (n = 11; 55%), followed by the non-AD and AD (30% and 20%, respectively). **A significant increase in cholinesterase inhibitor treatment was observed after [AB] PET (+218%, 34 patients before and 108 patients after).**" Leuzy A, Savitcheva I, Chiotis K, et al. Eur J Nucl Med Mol Imaging. 2019;46(6):1276-1286. doi:10.1007/s00259-019-04297-5.

17. *A Consecutive Case Series Experience with [18 F] florbetapir PET Imaging in an Urban Dementia Center: Impact on Quality of Life, Decision Making, and Disposition*. Concluding that "**Amyloid imaging provided novel and essential data that: (1) caused diagnosis to be revised; and/or (2) prevented the initiation of incorrect or suboptimal treatment; and/or (3) avoided inappropriate referral to an anti-amyloid clinical trial.**" Mitsis EM, Bender HA, Kostakoglu L, et al. Mol Neurodegener. 2014;9:10. Published 2014 Feb 3. doi:10.1186/1750-1326-9-10.

18. *Impact of Molecular Imaging on the Diagnostic Process in a Memory Clinic.* "**PET results led to a change in diagnosis in 35 (23%) patients**. This only occurred when prior diagnostic certainty was <90%. **Diagnostic confidence increased from 71 ± 17% before to 87 ± 16%**

after PET ($p < .001$)." Ossenkoppele R, Prins ND, Pijnenburg YA, et al. 2013;9(4):414-421. Alzheimers Dement. doi:10.1016/j.jalz.2012.07.003.

19. *Effectiveness of Florbetapir PET Imaging in Changing Patient Management*. When Aβ PET scans provided "immediate feedback," researchers found that for a "total of 618 subjects were randomized (1:1) to immediate or delayed feedback arms, and 602 subjects completed the 3-month primary endpoint visit. **A higher proportion of patients in the immediate feedback arm showed a change in diagnosis compared to the controls (32.6 vs. 6.4%; p = 0.0001). Similarly, a higher proportion of patients receiving immediate feedback had a change in management plan (68 vs. 55.5%; p < 0.002)**, mainly driven by changes in AD medication. Specifically, acetylcholinesterase inhibitors were prescribed to 67% of the amyloid-positive and 27% of the amyloid-negative subjects in the information group compared with 56 and 43%, respectively, in the control group ($p < 0.0001$). Pontecorvo MJ, Siderowf A, Dubois B, et al. Dement Geriatr Cogn Disord. 2017;44(3-4):129-143. doi:10.1159/000478007.

20. *Incremental Value of Amyloid-PET Versus CSF in the Diagnosis of Alzheimer's Disease*. "Among patients with a pre-biomarker diagnosis of AD, negative **PET induced significantly more diagnostic changes than amyloid-negative CSF** at both rounds 2 (CSF 67%, PET 100%, P = 0.028) and 3 (CSF 0%; PET 78%, P < 0.001); **PET induced a diagnostic confidence increase significantly higher than CSF** on both rounds 2 and 3." Ramusino MC, Garibotto V, Bacchin R, et al. Eur J Nucl Med Mol Imaging. 2020;47(2):270-280. doi:10.1007/s00259-019-04466-6.

21. *Practical Utility of Amyloid and FDG-PET in an Academic Dementia Center*. **"The primary diagnosis changed after PET in 13/140 patients (9%) overall but in 5/13 (38%) patients considered pre-PET diagnostic dilemmas."** Sánchez-Juan P, Ghosh PM, Hagen J, et al. Neurology. 2014;82(3):230-238. doi:10.1212/WNL.0000000000000032.

22. *Impact of Beta-Amyloid-Specific florbetaben PET Imaging on Confidence in Early Diagnosis of Alzheimer's Disease*. "In 18% of patients who had initially received the diagnosis of probable AD, PET scans were rated negative, whereas in controls 18% of scans were positive. **An increase in confidence in the initial diagnosis was frequently reported (80%). Imaging results had a significant impact on the intended patient care, as judged by the referring physicians:** this was most prominent in those patients with a contradicting scan and/or a low confidence in the initial diagnosis." Schipke CG, Peters O, Heuser I, et al. Published correction appears in Dement Geriatr Cogn Disord. 2012;34(3-4):262]. Dement Geriatr Cogn Disord. 2012;33(6):416-422. doi:10.1159/000339367.

23. *Amyloid-Positronenemissionstomographie mit [18 F]-Florbetaben in der Demenzdiagnostik [Amyloid Positron-Emission-Tomography with [18 F]-florbetaben in the Diagnostic Workup of Dementia Patients]*. "**Overall, in 7 out of 33 examined patients the initial diagnosis had to be changed because of the findings of the FBB-PET scan**." Schönecker S, Prix C, Raiser T, et al. Nervenarzt. 2017;88(2):156-161.

24. *Impact of (18)FDG PET and (11)C-PIB PET Brain Imaging on the Diagnosis of Alzheimer's Disease and Other Dementias in a Regional Memory Clinic in Hong Kong.* Researchers found that "**diagnosis was subsequently changed in 36.3% of subjects following PET.**" Shea YF, Ha J, Lee SC, Chu LW. Hong Kong Med J. 2016;22(4):327-333. doi:10.12809/hkmj154707.

25. *Utility of Amyloid PET Scans in the Evaluation of Patients Presenting with Diverse Cognitive Complaints.* The impact of amyloid PET imaging was studied in 102 patiets presenting at a memory clinic in Florida. **Following Aβ-PET, changes were made in diagnosis (37.3%), in specific treatments for Alzheimer's disease (26.5%) and in psychiatric treatments (25.5%).** The agreement between diagnosis pre-Aβ-PET versus post-A_-PET diagnosis was only fair, with a Cohen's kappa of 0.23 (95% CI 0–0.42). Shea YF, et al. J Alzheimers Dis. 2018.

26. *The Incremental Diagnostic Value of [18F]Florbetaben PET and the Pivotal Role of the Neuropsychological Assessment in Clinical Practice*. "There were 69/104 (66%) [18F]florbetaben positive scans, 51/62 (82%) patients were suspected as having AD before the PET scan and 18/42 (43%) were not. **Overall, the data obtained at PET changed 18/104 diagnoses (17%) and increased diagnostic confidence from 69.1±8.1% to 83.5±9.1 ($p < 0.001$)**, with the greatest impact on diagnosis and confidence in PET negative patients with an initial diagnosis of AD ($p < 0.01$) and in early-onset patients ($p = 0.01$). Spallazzi M, Barocco F, Michelini G, et al. J Alzheimers Dis. 2019;67(4):1235-1244. doi:10.3233/JAD-180646.

27. *Impact of Amyloid-PET in Daily Clinical Management of Patients with Cognitive Impairment Fulfilling Appropriate Use Criteria*. In a study designed to "evaluate the use of amyloid-positron emission tomography (PET) in routine clinical practice" researchers found "**the therapeutic intention was modified in 93 patients (44.1%) [after using Aβ PET]**" and found that provider confidence pre-scan and post-scan varied significantly. Triviño-Ibáñez EM, Sánchez-Vañó R, Sopena-Novales P, et al. Medicine (Baltimore). 2019;98(29).

28. *Added Value and Limitations of Amyloid-PET Imaging: Review and Analysis of Selected Cases of Mild Cognitive Impairment and Dementia*. **In a retrospetive review of 16 cases, this study reported a change in diagnosis in 11 cases and a change in AD treatment in 10.** Weidman DA, Zamrini E, Sabbagh MN, et al. Neurocase. 2017;23(1):41-51. doi:10.1080/13554794.2017.1290806.

29. *Diagnosing Dementia in the Clinical Setting: Can Amyloid PET Provide Additional Value Over Cerebrospinal Fluid?* "Twenty patients from a cognitive clinic, who had undergone detailed assessment including CSF measures, went on to have amyloid PET. The treating neurologist's working diagnosis, and degree of diagnostic certainty, was assessed both before and after the PET. **Amyloid PET changed the diagnosis in 7/20 cases**. Amyloid PET can provide added diagnostic value, particularly in young-onset, atypical dementias, where CSF results are borderline and diagnostic uncertainty remains." Weston PS, Paterson RW, Dickson J, et al. J Alzheimers Dis. 2016;54(4):1297-1302. doi:10.3233/JAD-160302.

30. *Impact of ^{18}F-florbetapir PET Imaging of β-amyloid Neuritic Plaque Density on Clinical Decision-Making.* "We present 11 cases (age range 67-84) of cognitively impaired subjects in whom clinician surveys were done before and after PET scanning to document the theoretical impact of amyloid imaging on the diagnosis and treatment plan of cognitively impaired subjects. Subjects have been clinically followed for about 5 months after the PET scan. Negative scans occurred in five cases, **leading to a change in diagnosis for four [of 11] patients and a change in treatment plan for two [of 11] of these cases.** Positive scans occurred in six cases, **leading to a change in diagnosis for four [of 11] patients and a change in treatment plan for three [of 11] of these cases.**" Zannas AS, Doraiswamy PM, Shpanskaya KS, et al. Neurocase. 2014;20(4):466-473. doi:10.1080/13554794.2013.791867.

31. *Diagnostic Value of Amyloid Imaging in Early Onset Dementia*. **Amyloid PET scans resulted in diagnostic change in 20% of the amyloid-positive cases and physicians' confidence in their clinical diagnosis increased from 76% to 90%**. M.D. Zwan, F.H. Bouwman, W. VdF, A. Lammertsma, B. van Berckel, P. Scheltens. Alzheimers Dement. 10: 2014; 14.

These studies demonstrate that Aβ PET contributes to diagnostic revisions in approximately 30% of patients and increases diagnostic confidence in approximately 60% of subjects. Overall changes in management were observed in 32% to 87% of patients. The most common type of change in management was either the initiation or discontinuation of planned AD medication: medication changes were observed in approximately 40% of patients. Other types of management changes included referral to clinical trials, AD genetic testing, addition or removal of planned diagnostic tests, and counseling. These data have consistently demonstrated how the knowledge of amyloid status adds value to the management of patients, including minimizing misdiagnosis. Moreover, changes to diagnosis and treatment management plans, even without the disease modifying agents available or in development, most likely improve patient outcomes because they reduce adverse events due to potentially inappropriate treatment and increase the chances that a patient receives the correct care. Accordingly, CMS must abandon any coverage criterion conditioned on further evidence development and should close the book on the further delays to Medicare beneficiary access to Aβ PET scans.

III. CMS Should Eliminate Lifetime Limits on the Number of Beta Amyloid PET Scans

CMS's stated basis for establishing a coverage limit of one scan per lifetime was:

> However, there is sufficient evidence that the use of PET Aβ imaging is promising in two scenarios: (1) to exclude Alzheimer's disease (AD) in narrowly defined and clinically difficult differential diagnoses, such as AD versus frontotemporal dementia (FTD); and (2) to enrich clinical trials seeking better treatments or prevention strategies for AD, by allowing for selection of patients on the basis of biological as well as clinical and epidemiological factors.
>
> Therefore, we will cover one PET Aβ scan per patient through coverage with evidence development (CED), under §1862(a)(1)(E) of the Act, in clinical studies that meet the criteria in each of the paragraphs below.[6]

While several of the studies cataloged above support CMS's first contention – namely, that Aβ PET can be useful in difficult differential diagnoses (cases similar to the Appropriate Use Criteria (AUC)) – several other studies demonstrate much broader clinical utility for Aβ PET. Specifically, in a meta-analysis of 13 studies, Shea et al. (*Impact of Amyloid PET Imaging in the Memory Clinic: A Systematic Review and Meta-Analysis.* Journal of Alzheimer's Disease 64 (2018) 323–335 DOI 10.3233/JAD-180239) reported that although the percentage of diagnostic change was higher in studies where Aβ PET was ordered in accordance with AUC criteria than where AUC criteria were not employed, "meta-regression did not show AUC accounting for variance of findings across the studies." Additionally, five studies that specifically compared retrospectively defined AUC-like and non-AUC like cases consistently found evidence of clinical utility in both AUC-like and non-AUC-like cases:

[6] CMS, NCD 220.6.20, *Beta Amyloid Positron Tomography in Dementia and Neurodegenerative Disease* (2013).

1. *Quantitative Appraisal of the Amyloid Imaging Taskforce Appropriate Use Criteria for Amyloid-PET.* Reported that "**AUC-like and non-AUC-like cases did not differ significantly in any outcome of clinical utility as assessed by the overlap of 95% AC-CI"**. Altomere et al., Alzheimers Dement, 2018. 14(8): p. 1088-1098.

2. *Critical Review of the Appropriate Use Criteria for Amyloid Imaging: Effect on Diagnosis and Patient Care.* Concluded that their "**results also suggest that patients who do not fall within the AUC are perhaps no less likely to benefit from amyloid imaging than patients meeting AUC**. In fact, in a typical clinical series of patients, they may have as a group more to gain overall from the information that amyloid imaging provides." Apostolova et al. *A*lzheimers Dement, 2016. 5: p. 15-22.

3. *Assessment of the Appropriate Use Criteria for Amyloid PET in an Unselected Memory Clinic Cohort: The ABIDE Project.* Reported that **in both AUC-consistent and AUC-inconsistent patients, post–positron emission tomography diagnosis (28%–21%) and management (32%–17%) change was substantial**. De Wilde et al. Alzheimers Dement. 2019 Nov;15(11):1458-1467.

4. *Effect of Amyloid Imaging on the Diagnosis and Management of Patients with Cognitive Decline: Impact of Appropriate Use Criteria.* Study noted above, reported that "**sixty-two percent of the AUC-like subjects had a change in diagnosis after scanning compared with 45% of the non-AUC subjects (p = 0.011). Both groups demonstrated high rates of change in their management plans after scanning (88.0% for AUC-like cases, 85.6% for non-AUC cases).**" Grundman et al. Dement Geriatr Cogn Disord, 2016. 41(1-2): p. 80-92, in a re-analysis of the Grundman et al., 2013.

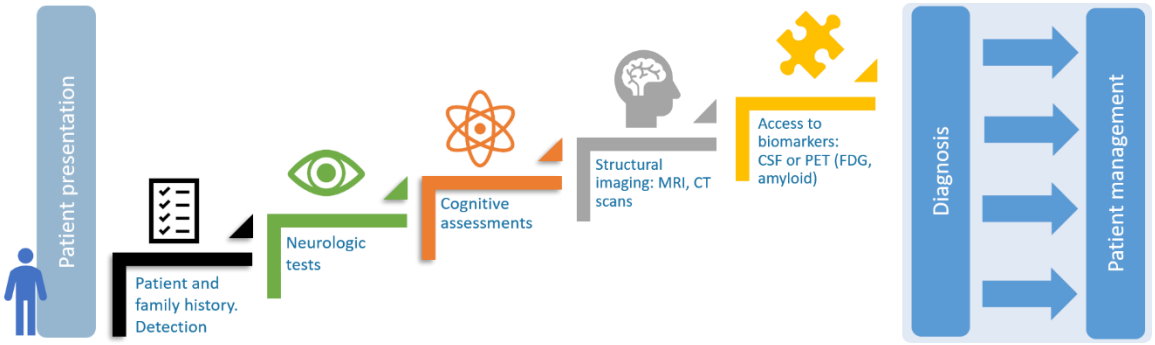
5. *Amyloid Imaging for Differential Diagnosis of Dementia: Incremental Value Compared to Clinical Diagnosis and [18F]FDG PET.* Reported **no significant difference between the percentage of AUC-like (21%) and non-AUC-like (27%) patients with a change in diagnosis post Aβ PET**. Hellwig et al., Eur J Nucl Med Mol Imaging. 2019;46(2):312-323.

And while it remains true that Aβ PET scans are useful to enrich clinical trials, the fact that several of those trials are now concluded and a therapeutic is available, with more likely in the very near future, CMS's second basis for limiting scan is also likely stale. Lilly's donanemab clinical trial, TRAILBLAZER-ALZ, demonstrates how treatment monitoring with Aβ PET can lead to the discontinuation of treatment with an amyloid-targeting therapy. Discontinuation potentially improves clinical and fiscal outcomes by reducing unnecessary use of therapeutics.

Lilly urges CMS to abandon any lifetime limit for all patients. Aβ PET imaging should be reasonable and necessary for patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD), including mild cognitive impairment due to AD (MCI-AD), or to assess response in those being treated with an FDA-approved anti-amyloid therapeutic. Additionally, it is important to note that while patients may have an Aβ PET scan that does not indicate AD pathology at one stage of their life, it is entirely possible that a repeat scan in future years could have a different result due to the nature of this disease.

Any concerns about overutilization of Aβ PET are unfounded. First, the scan process is inherently self-limiting. Patients would not actively seek out scans and providers do not liberally prescribe superfluous scans. Moreover, other diagnostic modalities, such as cognitive assessments and basic bloodwork, MRIs, CT scans limit the potential amount of patients for whom HCPs may seek to prescribe Aβ PET scans.

Figure 1: The Patient Diagnostic Journey



The AD research community recognizes and accepts a biomarker-based definition of AD, which is reflected in the most recent 2018 update to the National Institute on Aging-Alzheimer's Association (NIA-AA) research framework in which AD is seen as a continuum and the presence of the Aβ biomarker alone is characterized as "Alzheimer's pathologic change" as part of the very early stage of the AD continuum.[7] While not intended as diagnostic criteria or guidelines, the NIAA-AA framework is a leading indicator of where the field is headed and the critical importance of AD biomarkers in AD characterization. More recently, in 2021, the International Working Group recommended that the clinical diagnosis of AD be restricted to patients with "positive biomarkers" of AD in addition to specific AD symptoms, therein highlighting the importance of integrating AD biomarkers into clinical practice.[8]

As noted in the NIA-AA framework, "Studies published since 2011 have reinforced the idea that certain imaging and CSF biomarkers are valid proxies for neuropathologic changes of AD.[9] Imaging-to-autopsy comparison studies have established that amyloid positron emission tomography (PET) is a valid in vivo surrogate for Aβ deposits." Overall, the clinically approved tracers for Aβ imaging (further defined in the Design, Purpose, and Method of Use for Aβ PET Scans section below) demonstrate high sensitivity (range 88%-98%) and specificity (80%-95%) for detection of Aβ neuritic plaque pathology.

As Lilly has argued in previous comments, CMS should extend coverage for Aβ PET for beneficiaries with a clinical presentation consistent with the stage of disease identified in the FDA approved indication statements for amyloid targeting therapy who are being evaluated for diagnosis and potential treatment or continuation of treatment with an FDA-approved amyloid-targeting therapeutic.

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[7] Jack CR Jr, Bennett D, Blennow K, et al. *NIA-AA Research Framework: toward a biological definition of Alzheimer's disease*. Alzheimers Dement. 2018;14(4):535-562.
[8] Dubois B, Villain N, Frisoni GB, et al. *Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group.* Lancet Neurol. 2021 Jun;20(6):484-496. doi: 10.1016/S1474-4422(21)00066-1. Epub 2021 Apr 29. PMID: 33933186; PMCID: PMC8339877.
[9] *Id*.

IV. CMS Policies Disproportionately Impact Communities of Color and Should be Revised to Ensure Equitable Access to Aβ PET

Continuing to force patients to enroll in clinical trials to access Aβ PET undermines our shared goal of achieving health equity. As CMS is well aware, AD is marked by significant health disparities and inequities. Black Americans are nearly two times more likely, and Latinos are 1.5 times more likely to develop dementia compared to their White counterparts.[10] Despite this higher risk, Black Americans and Latinos are less likely to receive a timely diagnosis and are more likely to report discrimination as they attempt to access care for AD.[11,12]

These disparities in disease prevalence and access to a timely and accurate diagnosis are further magnified by the well document underrepresentation in and mistrust of medical research and clinical trials in the Black, Hispanic, Asian, and Native American communities. According to the Alzheimer's Association's Special Report on Race, Ethnicity, and Alzheimer's in America report, more than 60% of Black Americans believe that medical research is biased against minority communities, a view that is largely shared by Asian Americans (45%), Native Americans (40%), and Hispanic Americans (36%).[13]

These perceptions of bias directly influence interest in participating in clinical trials, with Black Americans being least interested (67%), followed by Asian Americans (73%), Hispanic Americans (78%), and Native Americans (81%).[14] Some of the most common reasons given for being unwilling to enroll in clinical trials include concerns about not wanting to be a "guinea pig," fears that treatment may result in illness, concerns regarding costs, as well as time and transportation implications.[15] Continuing to restrict access to Aβ PET to the clinical trial setting will only serve to exacerbate these long-standing fears regarding participating in clinical trials.

In fact, the original IDEAS study faced very similar challenges enrolling a representative patient population. As a result of these recruitment challenges, the administrators of IDEAS, the American College of Radiology and the Alzheimer's Association, developed a new study protocol designed specifically to measure the impact of amyloid PET scans in a more diverse patient population. New IDEAS is designed to enroll a total of 7,000 Medicare beneficiaries with the goal of at least half of participants self-identifying as Black/African American (at least 2,000 participants) and Latino/ Hispanic (at least 2,000 participants).[16,17]

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[10] Aranda, Maria P., Vega, William A., Richardson, Jason R., Resendez, Jason. "Priorities for Optimizing Brain Health Interventions Across the Life Course in Socially Disadvantaged Groups." Florida International University and UsAgainstAlzheimer's. (2019).
[11] Tsoy E, Kiekhofer R.E., Guterman E.L., et al., "Assessment of Racial/Ethnic Disparities in Timeliness and Comprehensiveness of Dementia Diagnosis in California." JAMA Neurol. (March 29, 2021). https://doi.org/10.1001/jamaneurol.2021.0399.
[12] Alzheimer's Association. "Race, Ethnicity and Alzheimer's in America." (2021). https://www.alz.org/media/Documents/alzheimers-facts-and-figures-special-report.pdf.
[13] *Id.* at 2.
[14] *Id.*
[15] *Id.*
[16] Alzheimer's Association. "Race, Ethnicity and Alzheimer's in America." (2021) at 2.
[17] New IDEAS Study Protocol, New IDEAS: Imaging Dementia—Evidence for Amyloid Scanning Study NCT04426539 (ClinicalTrials.gov). https://www.ideas-study.org/Getting-Started/Protocol.

To support the goal of diverse enrollment, New IDEAS also includes specific recruitment strategies to ensure that underrepresented populations participate, including partnerships with community members and healthcare providers in select metropolitan areas to encourage Black/African American and Latino participation. Notwithstanding a concerted effort to recruit a majority diverse patient population, as of June 2022, only 27% of study participants identified as Black, Hispanic, or Latino (14% Black/ African; 13% Hispanic/Latino).

Furthermore, minority patient enrollment in New IDEAS may be hindered by *patient misunderstanding of CED itself*. In recent interviews with New IDEAS minority recruitment team members in Tennessee and North Carolina, patient misunderstanding and confusion about CED-specifically the requirement to enroll in a clinical trial despite the fact that Aβ PET is FDA-approved-was identified as a recruitment barrier.[18]

We additionally urge CMS to, in parallel, address the issue of packaged payment for PET radiopharmaceuticals in the hospital outpatient department (HOPD) setting as this rate setting policy may discourage the use of advance diagnostics for AD in certain care settings. CMS's bundled payment policy for advanced radiopharmaceuticals in the hospital outpatient setting makes Aβ PET too cost prohibitive to even offer for many hospitals and doctors, especially those providing care to racial and ethnic minorities, who already face more significant delays in obtaining a timely and accurate diagnosis compared to their white counterparts. Indeed, a recent Government Accountability Office (GAO) report on package payment in Medicare Part B noted that the majority of hospitals invited to participate in the original IDEAS study for Aβ PET declined to participate in the New IDEAS study because "the packaged payment would cause them to incur a financial loss for each procedure performed."[19]

V. Conclusion

Lilly supports CMS's decision to reconsider the Aβ PET NCD and to modify the lifetime limit on the number of Aβ PET scans covered by Medicare. We further urge CMS to eliminate the CED requirements for Aβ PET coverage and we respectfully request that the following revisions be made to section (A) of 220.6.20 of the Medicare Coverage Determination Manual:

> The Centers for Medicare & Medicaid Services (CMS) has determined that the evidence is ~~insufficient~~ ***sufficient*** to conclude that the use of positron emission tomography (PET) beta amyloid (also referred to as amyloid-beta (Aβ)) imaging is reasonable and necessary ***under §1862(a)(1)(A) of the Social Security Act ("the Act")*** for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member for ***adult patients suffering from cognitive impairment who are being evaluated or treated for Alzheimer's disease and other causes of cognitive decline. In particular,*** Aβ PET imaging should be reasonable and necessary for patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD), including mild cognitive impairment due to AD (MCI-AD), or to assess response in those being treated with an FDA-approved anti-amyloid therapeutic. ~~Medicare beneficiaries with dementia or neurodegenerative disease, and~~

[18] New IDEAS Communications Committee.
[19] United States Government Accountability Office. Medicare Part B: Payments and Use for Selected New, High-Cost Drugs. March 2021. https://www.gao.gov/assets/gao-21-252.pdf.

~~thus PET Aβ imaging is not covered under §1862(a)(1)(A) of the Social Security Act ("the Act").~~

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In conclusion, Lilly appreciates this opportunity to present our comments on the proposed reconsideration of the national coverage for Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease. We are hopeful about the future of Alzheimer's care, and we urge CMS to revise its existing coverage policies to allow timely and appropriate access to the diagnostic tools that are necessary to identify patients who could most benefit from these therapies or who could benefit from discontinuation from therapy. We appreciate the time CMS has dedicated to meeting with us and other stakeholders, and we would be happy to answer any questions you have about these comments. Please contact Adam Phipps at phippsad@lilly.com or 614-256-6099 to discuss this letter.

Sincerely,

Anne E. White
President, Neuroscience Business Unit, Eli Lilly and Company