VIA ELECTRONIC FILING

November 7, 2022

Eli Lilly and Company

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Medicare Evidence Development & Coverage Advisory Committee
Attn: Tara Hall, MEDCAC Coordinator
Centers for Medicare & Medicaid Services, Center for Clinical Standards and Quality, Coverage and Analysis Group, S3–02–01,
7500 Security Boulevard,
Baltimore, MD 21244

Re: Medicare Program; Virtual Meeting of the Medicare Evidence Development and Coverage Advisory Committee—December 7, 2022

Dear Ms. Hall:

Eli Lilly and Company (Lilly) appreciates the opportunity to respond to the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) public notice regarding the December 7, 2022, public meeting examining requirements for clinical studies submitted for Centers for Medicare & Medicaid Services' (CMS) coverage requiring Coverage with Evidence Development (CED).[1] Lilly is one of the country's leading innovation-driven, research-based pharmaceutical and biotechnology corporations. Our company is devoted to seeking answers

for some of the world's most urgent medical needs through the discovery and development of breakthrough medicines and technologies and through the health information we offer. Ultimately, our goal is to develop products that save and improve patients' lives.

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 that permit the visualization of amyloid plaques and tau tangles—pathological hallmarks of AD—in the living brain, and continues development of disease-modifying treatments, including donanemab, which is currently under FDA review with an anticipated approval in early 2023. **CED has been particularly deleterious for patients living with AD** as access to both Beta Amyloid (Aβ) Positron Emission Tomography (PET) scans[2] and amyloid-targeted monoclonal antibody therapies[3] is subject to, and therefore limited by, CED.

I. CED Has Been Used to Delay Rather Than Expedite Coverage

[1] CMS, (2022, October 11). Medicare Program; Virtual Meeting of the Medicare Evidence Development and Coverage Advisory Committee-December 7, 2022. Retrieved November 7, 2022, from https://www.federalregister.gov/documents/2022/10/11/2022-22067/medicare-program-virtual-meeting-of-the-medicare-evidence-development-and-coverage-advisory
[2] CMS, NCD 220.6.20, Beta Amyloid Positron Tomography in Dementia and Neurodegenerative Disease (2013).
[3] CMS, CAG-00460N, Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (2022).

As MEDCAC evaluates the recent report released by the Agency for Healthcare Research and Quality (AHRQ), Lilly would like to share concerns we have regarding the approach AHRQ has taken in this effort. While AHRQ stated that "[CED] is intended to expedite beneficiary access to innovative items and services…"[4] Lilly believes that the actual application of CED has resulted in the opposite effect, by restricting access to a much narrower pool of patients than the FDA-approved indications, thus undermining efforts to meet unmet need and significantly delaying meaningful patient access to drugs which have already established clinical meaningfulness through drug-development clinical trials. Further, while we think developing sound standards for study design and evidence generation is an important task and ensuring sound study design is particularly important in the context of a policy like CMS' CED policy, we strongly believe MEDCAC should take a step back and consider the fundamental question of whether CED, in its current form and application, accomplishes the stated goal of efficiently providing patients access to new therapies while continuing to learn about them.

One recent example of the CED paradigm failing to live up to its stated aim is the ongoing of CED restrictions for Aβ PET. The existing evidence regarding the value of Aβ PET scans overwhelmingly demonstrates the reasonableness and necessity of these tests. The Aβ PET CED NCD, which was published in 2013, is nearly a decade old and has not kept pace with data generation and clinical developments in AD. Since 2013, **more than 30 peer-reviewed studies**[5] have empirically and repeatedly demonstrated significant clinical utility by causing changed clinical management, changed patient diagnoses, and improved provider confidence. Even with an open NCD reconsideration plus the recent announcement of positive topline data for an amyloid-targeting, disease-modifying therapy for patients suffering from AD, CMS has chosen to not even include CED within the scope of the NCD reconsideration. Despite the extensive evidence that Aβ PET provides clinical value in the absence of disease-modifying medications, and now the multiplication of value that is derived when supporting appropriate patient identification and potentially treatment monitoring for patients being treated with amyloid-targeting therapies, and the repeated requests of stakeholders in the Alzheimer's community (See Appendix A), CMS has yet to reassess the need for CED. This is contrary to CMS's own principles for CED, which state that "CED will not be used when less restricted coverage is justified by the available evidence" and that "CED will generally expand access to medical technologies for beneficiaries."[6]

We believe that continued CED limitations on coverage for Aβ PET are unnecessary, inappropriate, and inconsistent with CMS' principles for CED. CED should not be used to deny patients access to well established, widely accepted diagnostic tools that have been demonstrated through years of

[4]Lilly continues to maintain that CMS lacks the statutory authority to impose CED requirements in the manner set forth by the AB PET and the Alzheimer's therapeutic NCDs. We encourage AHRQ 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 ARHQ 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.

[5] https://www.cms.gov/files/document/whitecomment07152022pdf.pdf

[6] CMS, Guidance for the Public, Industry, and CMS Staff: Coverage with Evidence Development (Nov. 20, 2014).

research to have an important role in diagnosing, managing, and assessing potential treatment options for Medicare patients with dementia and neurodegenerative disease.

II. CED Has Exacerbated Health Disparities

We are also concerned and would like to highlight that CMS' payment policy for amyloid PET scans may be exacerbating existing health disparities in AD. Black Americans and Hispanic Americans are more likely to have suspected Alzheimer's Disease and other dementias but are less likely to be diagnosed than White Americans.[7] Diagnosis among minority groups is also delayed, with a lower percent of patients diagnosed in the mild cognitive impairment stage among Black (18 percent), Hispanic (16 percent), and Asian (12 percent) than White patients (23 percent).[8] Expanding access to scans in the hospital outpatient setting, for example, could help to remedy these disparities and provide more equitable access to care at an earlier stage of the disease, when amyloid-targeting therapies are most likely to be effective. Further, CED severely limits treatment for the majority of beneficiaries who live outside of major U.S. cities.[9] There is significant research that highlights the negative connection between geographic access to care and travel time.[10] A recent analysis demonstrated that restricting therapeutic access to trial sites disproportionately impacts access for populations already inordinately impacted by Alzheimer's disease. [11]

AHRQ missed an opportunity to address many of the problems with the current CED paradigm, specifically, by not asking the fundamental question of whether it achieves the goal of improving rather than restricting patient access, while collecting the minimum necessary data to make a coverage determination based on CMS' Reasonable & Necessary criteria. Indeed, a recent study of CED programs demonstrates some of the inefficiencies and access barriers that exist in the CED paradigm.[12] Out of the 27 CED programs reviewed, only four had resulted in retirement, and the time from initiation to retirement of CED ranged from 4 to 12 years. Therefore, Lilly strongly advocates that MEDCAC re-evaluate CMS' approach and to assess if the CED program is operating as intended and transparently seek input on ways to improve how and when CED should be used. Only then would it be appropriate to re-evaluate the study requirements for CED.

III. CED Processes Are Opaque and Stakeholder Input is Rarely Solicited or Acted On

Finally, Lilly had serious concerns with the overall approach that AHRQ used for their current report, including lack of transparency surrounding this process and the approach to gathering

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[7] Alzheimer's Association, 2021 Alzheimer's Disease Facts And Figures, at 25-26, https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf.

[8] Tsoy E, et al., Assessment of Racial/Ethnic Disparities in Timeliness and Comprehensiveness of Dementia Diagnosis in California. JAMA Neurol. 2021;78(6):657-665. doi:10.1001/jamaneurol.2021.0399.

[9] Grogan, J. (2022) CMS's Alzheimer's coverage policy will inhibit access and discourage innovation, USC Schaeffer. Available at: https://healthpolicy.usc.edu/evidence-base/cmss-alzheimers-coverage-policy-will-inhibit-access-and discourage-innovation/.

[10] Bosanac, E. M., Parkinson, R. C., & Hall, D. S. (1976). Geographic Access to Hospital Care: A 30-Minute Travel Time Standard. *Medical Care*, *14*(7), 616–624. http://www.jstor.org/stable/3763774

[11] Grogan, J. (2022) CMS's Alzheimer's coverage policy will inhibit access and discourage innovation, USC Schaeffer. Available at: https://healthpolicy.usc.edu/evidence-base/cmss-alzheimers-coverage-policy-will-inhibit-access-and-discourage-innovation/.

[12] Zeitler EP, Gilstrap LG, Colylewright M, et al. Coverage with evidence development: where are we now? AJMC. 2022;28(8).

input. The three-week comment period to respond to this notice was woefully insufficient, and we advocated for additional time for appropriate review and feedback – and reiterate that request as CED evaluation moves forward. This would be true regardless of the substance, but for such a highly technical subject, with broad impact, more time is needed to ensure robust and meaningful feedback. As MEDCAC moves forward with CED policy consideration, Lilly strongly encourages the committee advocate for agencies to submit guidance, delineating stakeholders involved, through the traditional Notice and Comment Period process which affords broader stakeholder participation.

Lilly appreciates the opportunity to engage with MEDCAC on this topic and looks forward to further discussions. Please contact Adam Phipps at phipps adam@lilly.com if you have any questions.

Sincerely,

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

Appendix A

October 31, 2022

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 submit this untimely comment on the proposed reconsideration of the coverage decision for Beta Amyloid Positron Emission Tomography (PET) in Dementia and Neurodegenerative Disease.[13] We appreciate that untimely comments are not guaranteed consideration by CMS, but we strongly encourage the agency to use its discretion to supplement the administrative record by expressly including and considering this comment, as there have been significant developments that bear upon the scope of the proposed CED reconsideration referenced in the tracking sheet.

Specifically, while we appreciate that stakeholders will have an opportunity to comment on a proposed decision memo later this year, **we believe it is important to supplement the administrative record now so that CMS may change the scope of the proposed CED reconsideration from a mere change on the lifetime limit for Aβ PET scans covered by Medicare under a CED paradigm to, instead, a comprehensive reconsideration inclusive of both the scan limit and the continued need for CED.**

Lilly and other stakeholders made this request in prior comments, but additional evidence published in the last month demonstrate – overwhelmingly – that Aβ PET is reasonable and necessary, and that Alzheimer's patients cannot – and should not – be denied coverage of these important diagnostic tools that clearly change treatment protocols and will doubtlessly ensure that timely therapies are initiated.

The Lecanemab Phase III Confirmatory Data (CLARITY AD) Provides Incontrovertible Evidence that Aβ PET Scans Are Reasonable and Necessary.

[13] 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.

On September 27, Eisai and Biogen announced topline results from the CLARITY AD study.[14]. While the pendency of that study was known to CMS and highlighted by stakeholders in July, the results were not yet known. The topline results are as follows:

- Lecanemab treatment met the primary endpoint and reduced clinical decline on the global cognitive and functional scale, Clinical Dementia Rating-Sum of Boxes (CDR-SB) compared with placebo at 18 months by 27%,
- All key secondary endpoints were also met with highly statistically significant results compared with placebo ($p<0.01$). Key secondary endpoints were the change from baseline at 18 months compared with placebo of treatment in amyloid levels in the brain measured by amyloid positron emission tomography (PET), the AD Assessment Scale-cognitive subscale14 (ADAS-cog 14), AD Composite Score (ADCOMS) and the AD Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL).
- Eisai will present the Clarity AD study results on November 29, 2022, at the Clinical Trials on Alzheimer's Congress (CTAD), and publish the findings in a peer-reviewed medical journal.

Importantly, one of the inclusion criteria for this trial was proof of amyloid pathology in the brain. To obtain this proof of pathology, Aβ PET scans were employed. While lecanemab has not been FDA approved and the precise requirements and instructions for use are not yet known, it is highly likely that Aβ PET scans will be one of the reasonable and necessary diagnostics either to commence or monitor therapy.

In the NCD for Beta Amyloid Positron Tomography in Dementia and Neurodegenerative Disease (220.6.20), published September 27, 2013, CMS stated, "The clinical usefulness of AD testing, including PET Aβ imaging, is limited by the current absence of therapies that meaningfully prevent, stabilize or reverse the progressive course of the condition. This leads to a corresponding limitation in the evidence that might be brought to bear on the impact of testing on meaningful clinical outcomes. Thus we have no evidence that PET Aβ imaging leads through informed physician management to the prevention, stabilization or reversal of AD."[15] With a positive registration-quality Phase 2 study for donanemab and now the positive Phase 3 study for lecanemab, and the potential upcoming FDA approval for both, this statement is no longer true. We encourage CMS to continue to monitor these developments and take necessary actions to bring the Beta Amyloid PET NCD current.

Additional Data Regarding Alzheimer's Diagnosis and Treatment is Imminent and Should Be Incorporated Within the NCD Reconsideration Analysis.

[14] Eisai Co., Ltd, News Release, LECANEMAB CONFIRMATORY PHASE 3 CLARITY AD STUDY MET PRIMARY ENDPOINT, SHOWING HIGHLY STATISTICALLY SIGNIFICANT REDUCTION OF CLINICAL DECLINE IN LARGE GLOBAL CLINICAL STUDY OF 1,795 PARTICIPANTS WITH EARLY ALZHEIMER'S DISEASE (Published September 28, 2022). Available at: https://www.eisai.com/news/2022/news202271.html

[15] CMS, CAG-00431N, NCD for Beta Amyloid Positron Tomography in Dementia and Neurodegenerative Disease (220.6.20) (Published September 27, 2013). Available at: https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=265

We appreciate that CMS needs to comply with certain timelines once a reconsideration is announced. However, several commenters have already alluded to imminent data releases. Such information includes, but is not limited to:

- The Department of Veteran Affairs (VA) recently published two studies focused on the role of Beta Amyloid PET imaging in the clinical care and management of patients within the VA. Independent of Lilly involvement, this research was led by Dr. Katherine Turk, a neurologist at the VA Boston Healthcare System. The researchers "hope their studies will lead to greater use of amyloid PET scans in VA and potentially outside of the agency, as well, if the policies of insurance companies change."[16]
- In early November, Lilly will announce topline results of TRAILBLAZER-ALZ 4, a head-to-head study of donanemab and aducanumab. The full results will be presented at the CTAD conference on November 30, 2022.
- The Alzheimer's Association is shortly expected to publish the results for Aim 2 of the IDEAS CED study for Beta Amyloid PET imaging. Aim 2 demonstrated a reduction in hospitalization rates for patients receiving a Beta Amyloid PET scan versus those who did not.
- A revised Appropriate Use Criteria (AUC) for Amyloid PET imaging is expected to be published before the end of the year. Multiple studies already demonstrate clinical utility of Beta Amyloid PET beyond the current AUC.

With such data available now or in the very near term, it is important for CMS to be comprehensive in this reconsideration of the Beta Amyloid PET NCD.

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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 emerging 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, Lilly Neuroscience
Eli Lilly and Company

[16] U.S. Department of Veterans Affairs, VA Research Currents, VA-led research finds PET scans important for ruling out Alzheimer's disease (Published September 26, 2022). Available at: https://www.research.va.gov/currents/0922-VA-led-research-finds-PET-scans-important-for-ruling-out-Alzheimers-disease.cfm