

July 11, 2022

Joseph Hutter, M.D.
Lead Medical Officer
Centers for Medicare and Medicaid Services

Electronically Submitted: CMS_caginquiries@cms.hhs.gov

Re: Public Comment on [NCA for Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease](#) (CAG-00431R)

Dear Dr. Hutter:

The American College of Radiology (ACR) representing more than 41,000 diagnostic radiologists, radiation oncologists, interventional radiologists, nuclear medicine physicians, and medical physicists, appreciates the opportunity to submit public comments in response to the Centers for Medicare and Medicaid Services' (CMS') National Coverage Analysis (NCA) for Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease. Our organization fully supports CMS initiating this NCD analysis to determine if the current policy of one scan per patient per lifetime should be revised.

The ACR strongly urges CMS to update its coverage of beta-amyloid PET not only for the purpose of diagnosis but also as a tool for therapeutic evaluation. The information presented below builds on this recommendation to further improve access to beta-amyloid PET imaging as a diagnostic tool for Alzheimer's Disease and to foster equitable care for those most at risk.

Currently, NCD 220.6.20 covers one PET amyloid-beta (A β) scan per patient in CMS-approved studies under coverage with evidence development (CED). ACR would like to present two recommendations to expand access and utility of beta-amyloid PET scans in clinical study protocols.

ACR supports removing the limit of one beta-amyloid PET scan per lifetime

Patients who are potential candidates for monoclonal antibodies should have an amyloid PET scan immediately before determining whether they are a candidate for monoclonal antibody therapy and before entering a covered trial. Amyloid status observed in earlier scans may no longer reflect a patient's current beta-amyloid status. Studies evaluating the use of blood biomarkers to determine amyloid status have noted that some patients who are positive by blood tests will initially be negative by PET but will ultimately "progress" to be positive by PET.¹ There is no evidence to suggest that a single amyloid PET scan per patient is appropriate or that an outdated scan can provide the diagnostic information needed to determine whether a patient is currently a candidate for therapy. Furthermore, ACR does not understand the scientific

¹ West T, Kirmess KM, Meyer MR, Holubasch MS, Knapik SS, Hu Y, Contois JH, Jackson EN, Harpstrite SE, Bateman RJ, Holtzman DM. A blood-based diagnostic test incorporating plasma A β 42/40 ratio, ApoE proteotype, and age accurately identifies brain amyloid status: findings from a multi cohort validity analysis. Molecular neurodegeneration. 2021 Dec;16(1):1-2

basis for limiting beta-amyloid PET to one scan per lifetime. Not only can CNS beta-amyloid status change over time, but ongoing clinical trials for monoclonal antibody therapies for AD have also used the results of post-treatment beta-amyloid PET to inform a decision on whether to continue monoclonal antibody therapy.

CMS should require post-treatment beta-amyloid PET to be performed as needed to document the removal of beta-amyloid PET from the brain

In addition to scans to determine a patient's eligibility for therapy, CMS should require and cover post-treatment PET scans to determine whether beta-amyloid has been removed. The Phase 2 Lilly trial for a monoclonal antibody under development (donanemab) required multiple post-treatment PET scans and participants were switched to the placebo if amyloid plaque levels fell below certain parameters.² If a therapy is targeting beta-amyloid, then CMS should require trial sites to use beta-amyloid PET pre-and post-treatment to assure accurate measurement of beta-amyloid burden. CMS should allow as many PET scans as are needed to ensure that the trial design is optimal and reliable and provides physicians the information needed to make informed decisions about initiating and continuing therapy. Notably, one or more scans during therapy to verify removal of amyloid must be covered.

The ACR agrees directionally with CMS's proposed decision to cover beta-amyloid PET for beneficiaries seeking access to an FDA-approved therapy targeting Alzheimer's Disease. However, we are disappointed that proposed coverage requirements limit broad access by aligning with CMS' almost decade-old NCD 220.6.20 and limiting coverage to only one beta-amyloid PET scan per beneficiary, who must also be enrolled in an approved CED clinical research study. We appreciate CMS revisiting NCD 220.6.20 and strongly urge CMS to expand access to gold-standard diagnostic imaging for populations most at risk for MCI and Alzheimer's dementia.

The ACR serves as the sponsor and operating center for the Imaging Dementia – Evidence for Amyloid Scanning (IDEAS) Study and subsequent New IDEAS Study. These studies are developed to address the CED requirements of CMS's 2013 NCD 220.6.20. A recently published primary analysis of the IDEAS study included 11,409 participants initially characterized as having mild cognitive impairment (MCI) or dementia of uncertain cause. 90 days after beta-amyloid 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, beta-amyloid PET was associated with substantial subsequent changes in the management of diagnostically challenging patients with cognitive disorders.³

Beyond the IDEAS study, at least 30 published studies involving more than 4,000 patients have reviewed the utility of beta-amyloid imaging for the diagnostic assessment of patients evaluated for cognitive impairment in memory clinics. Several meta-analyses and systematic reviews⁴ confirm the consistent impact of beta-amyloid PET in the evaluation of patients with cognitive impairment, demonstrating that beta-amyloid PET contributes to diagnostic revisions in approximately 30% of patients and increases

² Mintun, MA et al. Donanemab in Early Alzheimer's Disease. *New England Journal of Medicine*. 2021 May 6; 384: 1691-1704.

³ Rabinovici GD, Gatsonis C, Apgar C, et al. Association of Amyloid Positron Emission Tomography With Subsequent Change in Clinical Management Among Medicare Beneficiaries With Mild Cognitive Impairment or Dementia. *JAMA* 2019;321:1286-94

⁴ Barthel and Sabri, 2017, Fantoni et al., 2018, Shea et al., 2018, Kim et al., 2018

diagnostic confidence in approximately 60% of subjects. Changes in management were observed in 32% to 87% of patients, with the most common type of change in management being either the initiation or discontinuation of planned Alzheimer's disease medication. Medication changes were observed in approximately 40% of patients. Other types of management changes included a referral to clinical trials, Alzheimer's genetic testing, addition or removal of planned diagnostic tests, and counseling.

Coverage of beta-amyloid PET will increase patient access to this diagnostic tool. Currently, there are three FDA-approved radiopharmaceuticals for the identification of amyloid plaque in the brain: 18F florbetapir, 18F flutemetamol, and 18F florbetaben. These are currently covered (under CED) in the New IDEAS Study, a successor to the IDEAS Study, which is focused on minority populations. Outside of this trial, however, these tracers are not covered by CMS. It is essential that CMS find a mechanism to immediately cover beta-amyloid PET scans so that all Medicare beneficiaries have access. Without coverage for beta-amyloid PET, only those who can afford to pay full charges out of pocket or have the means to enroll in a CED study will have access, which will result in inequitable access.

The ACR requests that CMS reconsider the current NCD and develop national coverage for the use of beta-amyloid PET scans as a diagnostic test, as well as for the purpose of estimating beta-amyloid neuritic plaque density in adult patients who are being evaluated for Alzheimer's disease and other causes of cognitive decline or monitored during therapy.

The ACR appreciates the opportunity to submit comments to CMS on the NCD reconsideration for Beta Amyloid Positron Emission Tomography (PET) in Dementia and Neurodegenerative Disease. If you have any questions or comments on our letter, please do not hesitate to contact Charlie Apgar, Executive Vice President for Research, at capgar@acr.org.

Respectfully Submitted,



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Chief Executive Officer