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Submitted via email to: CAGinquiries@cms.hhs.gov

RE: Proposed Decision Memo for Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease (CAG-00431N)

Dear Dr. Jacques:

Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, strongly supports the Centers for Medicare & Medicaid Services' (CMS's) proposed evidence-based decision memo regarding coverage for positron emission tomography (PET) amyloid-beta (Aβ) imaging in dementia and neurodegenerative disease. The proposed CMS decision included the following conclusions and narrowly constructed circumstances under which CMS would provide coverage for such imaging:[1]

A. [CMS] proposes that the evidence is insufficient to conclude that the use of [PET] amyloid-beta (Aβ) imaging improves health outcomes for Medicare beneficiaries with dementia or neurodegenerative disease, and thus PET Aβ imaging is not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act ("the Act").

B. However, there is sufficient evidence that the use of PET Aβ imaging could be 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.

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[1] Centers for Medicare & Medicaid Services. Proposed decision memo for beta amyloid positron emission tomography in dementia and neurodegenerative disease (CAG-00431N). http://www.cms.gov/medicare-coverage-database/details/nca-proposed-decision-memo.aspx?NCAId=265. Accessed July 22, 2013.

> Therefore, we propose to 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.
>
> Clinical study objectives must be to (1) develop better treatments or prevention strategies for AD, or, as a strategy to identify subpopulations at risk for developing AD, or (2) resolve clinically difficult differential diagnoses (e.g., frontotemporal dementia (FTD) versus AD) where the use of PET Aβ imaging appears to improve health outcomes.
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> Clinical studies must be approved by CMS, involve subjects from appropriate populations, be comparative, prospective and longitudinal, and use randomization and postmortem diagnosis as the endpoint where appropriate. Radiopharmaceuticals used in the PET Aβ scans must be FDA approved. The studies must address one or more of the following questions. For Medicare beneficiaries with cognitive impairment suspicious for AD, or who may be at risk for developing AD:
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> 1. Do the results of PET Aβ imaging lead to improved health outcomes? Meaningful health outcomes of interest include: avoidance of futile treatment or tests; improving, or slowing the decline of, quality of life; and survival.
>
> 2. Are there specific subpopulations, patient characteristics or differential diagnoses that are predicitive [sic] of improved health outcomes in patients whose management is guided by the PET Aβ imaging?
>
> 3. Does using PET Aβ imaging in guiding patient management, to enrich clinical trials seeking better treatments or prevention strategies for AD, by selecting patients on the basis of biological as well as clinical and epidemiological factors, lead to improved health outcomes?

We strongly agree that there is a lack of adequate evidence to establish that PET Aβ imaging changes the health outcomes of patients displaying early symptoms or signs of cognitive dysfunction. Moreover, we are unaware of data from any completed, well-designed, controlled clinical trials evaluating whether PET Aβ imaging changes the health outcomes of any patient population. Therefore, we agree that PET Aβ imaging is not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act and that any coverage for such imaging in the Medicare beneficiary population should be strictly limited to well-designed clinical studies that satisfy the above-proposed criteria.

As you are aware, in an editorial in the *European Journal of Nuclear Medicine and Molecular Imaging*[2] and a subsequent critical review in the *Journal of Alzheimer's Disease*,[3] experts in the field of PET neuroimaging identified fundamental technological and practical problems with

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[2] Moghbel MC, Saboury B, Basu S, et al. Amyloid-β imaging with PET in Alzheimer's disease: Is it feasible with current radiotracers and technologies? *Eur J Nucl Med Mol Imaging.* 2012;39(2):202-208.

[3] Kepe V, Moghbel MC, Langstrom B, et al. Amyloid-β positron emission tomography imaging probes: A critical review. *J Alzheimers Dis.* May 6, 2013 [Epub ahead of print]. DOI:10.3233/JAD-130485.

PET Aβ imaging using radiotracers such as Avid Radiopharmaceuticals' florbetapir F 18 injection (Amyvid), the only radiotracer approved by the Food and Drug Administration (FDA) for such imaging. These problems include the following:

- There is a striking discrepancy between the distribution of Aβ deposits in the brain allegedly shown by florbetapir-PET scans in patients with Alzheimer's disease (AD) versus that seen with histopathological and immunohistochemical studies of brain samples from AD patients, which are the gold standards for identifying Aβ deposits.
- Imaging studies conducted with florbetapir, as well as virtually any other purported amyloid tracer, consistently have shown the frontal lobe to have one of the highest, if not the highest, standardized uptake values. In sharp contrast, autopsy studies of the brains of AD patients have demonstrated that the highest density of Aβ deposits was found in the temporal and occipital lobes, whereas the lowest concentration was seen in the limbic and frontal lobes.
- Likewise, multiple studies of other brain imaging modalities in AD patients revealed that the greatest degree of brain atrophy and abnormal metabolism occurred in the temporal and parietal lobes, whereas the lowest degree occurred in the frontal lobes.
- PET imaging with amyloid agents such as florbetapir shows substantial uptake in white matter of the brain, which is believed to be nearly devoid of Aβ plaques. Indeed, PET imaging with various purported amyloid agents consistently has shown higher ratios of white matter Aβ to grey matter Aβ than immunohistochemical tests. This pattern of white matter uptake of amyloid radiotracers such as florbetapir has been largely described as a product of nonspecific binding, but it has also been speculated to be an artifact of slower clearance rate due to reduced blood flow in the white matter as compared to grey matter.
- Given the size of Aβ plaques and the small percentage of total brain area occupied by Aβ plaques even in the most severely affected cortical regions, amyloid agents such as florbetapir almost certainly do not have sufficiently greater uptake in Aβ deposits than in the background to allow accurate detection of Aβ deposits on PET imaging.

Furthermore, a study measuring cerebral cortical uptake of florbetapir F 18 revealed substantial overlap in the range of uptake among the following three subject groups: patients with probable AD patients, patients with mild cognitive impairment, and older healthy controls.[4] Such performance characteristics of PET Aβ imaging predict that the test will have little clinical utility in evaluating patients with mild cognitive impairment or suspected early AD, the type of patients most likely to be offered such imaging.

Finally, data submitted to the FDA comparing the results of florbetapir-PET scans in a cohort of elderly end-of-life patients to staining results for brain Aβ at subsequent autopsies (the gold standard for detecting brain β-amyloid) revealed significant variability among readers

[4] Fleisher AS, Chen K, Liu X, et al. Using positron emission tomography and florbetapir F 18 to image cortical amyloid in patients with mild cognitive impairment or dementia due to Alzheimer disease. *Arch Neurol.* 2011;68(11):1404-1411.

interpreting the PET scans.[5] Five nuclear medicine physicians who were trained with Avid Radiopharmaceuticals' proposed web-based reader training program — the training methodology to be used for clinical implementation of the drug — were asked to retrospectively read florbetapir-PET scans in 59 subjects who subsequently underwent autopsy and staining for brain β-amyloid. The readers were instructed to use a binary reading system and classify each scan as either positive or negative. The median sensitivity among the five readers was 82 percent, with a range of 69 to 92 percent, and the median specificity was 95 percent, with a range of 90 to 95 percent.[6] The overall median error rate for the five readers was 14 percent, with a range of 8 to 22 percent.

Undoubtedly, when widely deployed in real-world settings, there will be significantly greater variability in reader training and skill as well as in the characteristics of the patient population for which florbetapir-PET brain imaging presumably is intended. As a result, the performance of the test in clinical practice will be substantially worse than that seen in the carefully controlled setting of a clinical trial.

Most important, even if there existed a perfectly accurate (100% sensitive and 100% specific) imaging for detecting brain Aβ deposits — and no such test does exist — such imaging would still lack clinical utility because: (a) brain Aβ deposits occur in multiple other pathologic conditions, including dementia with Lewy bodies, cerebral amyloid angiopathy, Parkinson's disease, Huntington's disease, and inclusion body myositis, as well as normal aging;[7,8,9,10] and (b) the currently available treatments for AD are ineffective in preventing progression of the disease and offer minimal clinically significant benefits in treating the signs and symptoms of the disease. Therefore, all patients being evaluated for cognitive impairment or early onset dementia should undergo the same thorough evaluation for possible reversible causes of impaired cognition or early dementia *regardless of whether they have a negative or positive imaging test for brain Aβ*.

In summary, we strongly recommend that CMS finalize its decision memo for PET Aβ imaging in dementia and neurodegenerative disease (CAG-00431N) as proposed, for the following reasons:

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[5] Feng Q. Center for Drug Evaluation and Research Clinical Review for NDA 202-008, Amyvid (florbetapir F 18 injection). March 7, 2012. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202008Orig1s000MedR.pdf. Accessed July 22, 2013.

[6] Eli Lilly and Company. Drug label for Amyvid (florbetapir F 18 injection) for intravenous use. Revised April 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202008s000lbl.pdf. Accessed July 22, 2013.

[7] Khachaturian ZS. Diagnosis of Alzheimer's disease. *Arch Neurol.* 1985;42(11):1097-1105.

[8] The Food and Drug Administration. Summary minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting. October 23, 2008. http://www.fda.gov/ohrms/dockets/ac/08/minutes/2008-4382m1-Final.pdf. Accessed July 22, 2013.

[9] Eli Lilly and Company. Drug label for Amyvid (florbetapir F 18 injection) for intravenous use. Revised April 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202008s000lbl.pdf. Accessed July 22, 2013.

[10] Centers for Medicare & Medicaid Services. Proposed decision memo for beta amyloid positron emission tomography in dementia and neurodegenerative disease (CAG-00431N). http://www.cms.gov/medicare-coverage-database/details/nca-proposed-decision-memo.aspx?NCAId=265. Accessed July 22, 2013.

(1) There are no data from any completed, well-designed, controlled clinical trials evaluating whether PET imaging of brain Aβ changes the health outcomes of patients who display early symptoms or signs of cognitive dysfunction, or in any other patient population.
(2) There is a lack of correlation in AD patients between the areas of the brain showing a positive signal on PET Aβ scans and those areas of the brain having the highest density of Aβ deposits at autopsy.
(3) Interpretation of brain Aβ PET scans is subject to significant variability among readers.
(4) The results of brain Aβ PET scans currently have no clinical utility because the results of such imaging should have no impact on the clinical evaluation of patients with cognitive impairment or early onset dementia.

Thank you for considering our comments regarding this important issue.

Sincerely,

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