

March 15, 2013

Patrick Conway, MD, MSc.
Chief Medical Officer for the Centers for Medicare & Medicaid Services
Director of the Center for Clinical Standards and Quality
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

Re: National Coverage Analysis (NCA) for Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease

Dear Dr. Conway,

We, the undersigned, experts in Alzheimer's disease and brain imaging, are writing on behalf of the patients and families we serve to advocate for CMS coverage for amyloid PET imaging in the diagnosis of progressive cognitive decline. We join with patient advocacy groups including the Alzheimer's Association and the Alzheimer's Drug Discovery Foundation, and professional organizations including the Society of Nuclear Medicine and Molecular Imaging, World Molecular Imaging Society, and the Medical Imaging and Technology Alliance to recommend CMS approval of amyloid PET imaging when its use follows the published appropriate use criteria.¹

The foundation of good medical practice is based on accurate diagnosis. Patients and families want and need to know the cause of the loss of their memory, language, and thinking abilities. Currently, a substantial percentage of patients with cognitive impairment, possibly due to Alzheimer's disease (AD), do not receive the correct diagnosis. Amyloid PET is a major advance in the diagnosis and treatment of AD. Previously, we had to wait for a post-mortem examination to definitively diagnose AD. Now, with amyloid PET, we are able to safely and reliably detect fibrillar forms of amyloid, one of the hallmarks of AD.

The FDA set rigorous standards for the approval of amyloid PET imaging. They required that the abnormalities seen on PET closely correlate with neuritic amyloid pathology seen post-mortem. The results of imaging vs. post-mortem studies with Amyvid met those rigorous standards, leading to FDA approval of Amyvid for imaging of amyloid pathology in 2012.

To provide guidance to dementia care practitioners, patients, and caregivers, the Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging convened the Amyloid Imaging Taskforce (AIT). The AIT considered a broad range of specific clinical scenarios in which amyloid PET could potentially be used appropriately. Peer-reviewed, published literature was searched to ascertain available evidence relevant to these scenarios, and the AIT developed a consensus of expert opinion. A set of specific appropriate use criteria (AUC) were agreed on that define the types of patients and clinical circumstances in which amyloid PET could be used.

These criteria recommend the use of brain amyloid imaging in those patients already experiencing cognitive impairment. It is important to note, in light of some confusion at the January 2013 MEDCAC meeting, that the AUC do not support (nor do we) its use in asymptomatic patients or those with only subjective complaints. Furthermore, amyloid imaging does not substitute for a careful history and examination. In fact, the history and examination are required to understand the clinical context necessary to incorporate imaging results into clinical decision making. As is almost always the case, imaging is only one tool among many that clinicians should use judiciously to manage patients.

The utility of amyloid imaging is greatest in patient populations with objectively confirmed cognitive impairment, but of uncertain diagnosis despite thorough examination by a dementia expert. In such a setting, the expectation is that an amyloid scan would increase diagnostic certainty and alter clinical management.

According to those criteria, appropriate candidates for amyloid PET imaging include:

- Those who complain of persistent or progressive unexplained memory problems or confusion **and** who demonstrate impairments using standard tests of cognition and memory. That is, patients with persistent or progressive unexplained mild cognitive impairment (MCI).
- Individuals with dementia meeting criteria for possible Alzheimer's Disease, but who are unusual in their clinical presentation (either an atypical clinical course or an etiologically mixed presentation).
- Individuals with progressive dementia and atypically early age of onset (before age 65).

We strongly support the AUC recommendations that amyloid imaging be considered as part of a comprehensive evaluation by a dementia expert in patients with objectively determined cognitive impairment and limiting the use of amyloid PET to the 3 groups of patients listed above. The application of these criteria will restrict the use of this test to patients most likely to benefit.

A dementia expert (as referred to above), typically a neurologist, geriatric psychiatrist, or geriatric medicine specialist, has formal training and/or extensive clinical experience in dementia treatment and devotes a substantial percentage of their clinical practice to the diagnosis and treatment of dementia.

MCI (as indicated in the AUC) refers to progressive cognitive decline that is still mild with only limited interference with the ability to work or carry out activities of daily living. In the case of MCI, an amyloid PET finding of positivity would, on the basis of its known correspondence to brain beta amyloid plaques, raise the level of certainty that the patient's mild impairment is on the basis of AD pathology and represents early AD dementia. A negative scan in patients with MCI whose clinical picture may be complicated by vascular, inflammatory, traumatic, psychiatric or medical factors would make AD pathology an unlikely cause of their cognitive impairment. However, it is important to emphasize that not all patients with MCI would be appropriate for amyloid PET. The AUC criteria clearly recommend, "Amyloid PET would be appropriate only in those individuals who the dementia expert has concluded would benefit from greater certainty of

the underlying pathology and whose clinical management would change as a result of this greater certainty.”

There is evidence that including amyloid imaging in a comprehensive evaluation of cases with diagnostic uncertainty increases diagnostic confidence and affects treatment planning.³⁻⁵ The following 2 case examples help illustrate the impact of amyloid PET imaging in cases of diagnostic uncertainty.

Case 1 MCI: A 67 year old woman working as an office cleaner had a one year history of short-term memory difficulty and depression. She was living alone, driving, and working full-time. There was a history of dementia in her mother and brother. A brain MRI was normal. Cognitive testing revealed an isolated deficit in short-term memory. Amyloid PET imaging with Amyvid was clearly positive. The diagnosis was amnesic MCI due to Alzheimer’s disease. Her sister began assisting with her finances and moved in with her for companionship and support. The patient was begun on a cholinesterase inhibitor and referred for a treatment trial of amyloid-lowering medication to try and slow the progression of cognitive decline. Treatment planning would have been quite different if her amyloid PET scan had been negative.

Case 2 Atypical presentation with co-morbidity: An 85 year old woman, living alone in senior housing, was evaluated for memory loss, depression, and gait impairment. MRI scan of the brain revealed ventricular enlargement, cerebral atrophy, and extensive deep white matter lesions. Cognitive testing showed mild dementia with amnesia and executive impairment. The diagnosis was possible Alzheimer’s disease complicated by cerebrovascular disease and communicating hydrocephalus. An Amyvid PET scan showed significant amyloid binding consistent with AD. The patient was started on a cholinesterase inhibitor, advised to discontinue driving, and her daughter began overseeing her medications and finances. The results of the examination, amyloid scan, and MRI indicated that hydrocephalus was not playing a major role in her functional decline and shunt surgery was not recommended.

The AUC makes additional recommendations to further delineate *inappropriate* use of amyloid imaging: 1) patients with core clinical criteria for probable AD with typical age of onset; 2) to determine dementia severity; 3) based solely on a positive family history of dementia or presence of APOE-ε4; 4) patients with a cognitive complaint that is unconfirmed on clinical examination; 5) in lieu of genotyping for suspected autosomal mutation carriers; 6) in asymptomatic individuals; and 7) nonmedical use (e.g., legal, insurance coverage, or employment screening). We concur that amyloid imaging is not indicated in any of these circumstances based on evidence available at this time.

We believe that early and accurate diagnosis of Alzheimer’s disease is important and clinically meaningful. It leads to better outcomes and higher quality of life for people with Alzheimer’s Disease and their families by: enabling earlier access to appropriate treatments, allowing the family to build a care team and seek out education and support services, providing access to approved medications, enabling enrollment in Alzheimer’s/dementia clinical trials, and providing an opportunity for the development of advance directives and financial planning. These choices represent health outcomes, and the beneficial effect of early and accurate

diagnosis enhanced by amyloid imaging is a substantial improvement in outcome for which Medicare Beneficiaries deserve covered access.

Amyloid PET imaging is an unprecedented medical advance that provides an early milestone in meeting the major goal of the National Plan to Address Alzheimer's Disease, announced last year by Secretary Sebelius, to make major strides in the diagnosis and treatment of AD by 2025. Restricting its use to dementia experts and specific patient populations, as outlined in the AUC, will avoid misuse and excessive cost. CMS already requires similar limitations for FDG PET.

In summary, accurate diagnosis to improve health outcomes for people with cognitive impairment and their families is both reasonable and necessary for Medicare beneficiaries. We recommend that CMS approve PET amyloid imaging via a National Coverage Decision with immediate effect. This opportunity is of major importance to patients, their families and caregivers, dementia experts, and all physicians and health care professionals who deal with patients experiencing cognitive impairment. We appeal to CMS to consider the information provided in this letter as well as the abundance of other data, expert opinion and perspectives supplied by other groups and organizations in support of providing Medicare beneficiaries access to this class of imaging procedures.

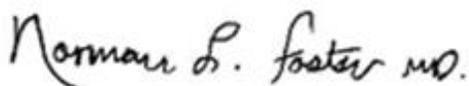
Sincerely,



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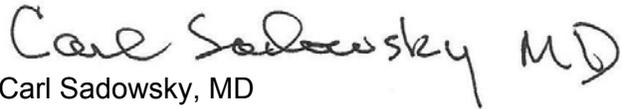
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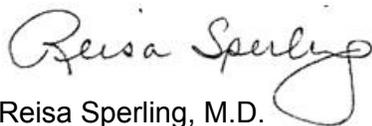
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References

- 1) Johnson, KA, Minoshima, S, Bohnen, NI, et al. Appropriate Use Criteria for Amyloid PET; A Report of the Amyloid Imaging Task Force, The Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. *J Alzheimers & Dementia* 2013; 54:1-15)
- 2) Buchhave P, Minthon L, Zetterberg H, Wallin A, Blennow K, Hansson O. Cerebrospinal Fluid Levels of β -Amyloid 1-42, but Not of Tau, Are Fully Changed Already 5 to 10 Years Before the Onset of Alzheimer Dementia. *Arch Gen Psychiatry*. 2012;69(1):98-106
- 3) Grundman, M, Pontecorvo, MJ, Salloway, SP, et al. Potential Impact of Amyloid Imaging on Diagnosis and Intended Management in Patients with Progressive Cognitive Decline. *Alz Dis Assoc Disord* 2013 Jan; 27 (1):4-15
- 4) Ossenkuppele, R, Prinsa, ND, Pijnenburga, YAL, et al. Impact of Molecular Imaging on the Diagnostic Process in a Memory Clinic. *Alzheimers Dement* 2012 Nov 16; Epub ahead of print.
- 5) Schipke, CG, Peters, O, Heuserb, I, et al. Impact of Beta-Amyloid-Specific Florbetaben PET Imaging on Confidence in Early Diagnosis of Alzheimer's Disease. *Dement Geriatr Cogn Disord* 2012; 33(6):416-22.
- 6) Doraiswamy PM, Sperling RA, Coleman RE, et al. Amyloid- β assessed by florbetapir F 18 PET and 18-month cognitive decline: A Multicenter Study. *Neurology* 2012;79:1-12. Epub ahead of Print July 11, 2012
- 7) Okello A, Koivunen J, Edison P, et al. Conversion of amyloid positive and negative MCI to AD over 3 years: An 11C-PIB PET study. *Neurology* (2009) 73 (10): 754-760

Conflicts of Interest Relevant to Amyloid Imaging

Devous:	institutional research or clinical trial support (Avid, >\$5K); consulting, advisory committee or speaker honoraria (Lilly >\$5K; <\$5K each: Navidea, Piramal, GE Healthcare); no stock ownership, royalties, or patents.
Salloway	institutional research support (GE Healthcare and Avid-Lilly, >\$5K); attended the MEDCAC meeting on amyloid PET on 1/30/13 at his own expense; consulting, advisory committee or speaker honoraria (GE Healthcare, Avid, Lilly <\$5K); no stock and has no patents or royalties related to research being conducted on Alzheimer's disease.
Foster	Institutional research or clinical trial support (Avid/Lilly, GE Healthcare, Center for Health Improvement, Janssen Alzheimer Immunotherapy, each>\$5K); Consulting, advisory committee or speaker honoraria (Lilly, Web MD, World Molecular Imaging Society each<\$5K; Bristol-Myers Squibb >\$5K); No stock ownership, royalties, or patents.
Fillit	None
Sadowsky	institutional research or clinical trial support (Lilly, >\$5K); consulting, advisory committee or speaker honoraria (<\$5K each: Novartis, Accera, Lilly, Pamlab); no stock ownership, royalties, or patents.
Johnson:	consulting, advisory committee or speaker honoraria (<\$5K each: GE Healthcare, Siemens, Avid, Lilly, Piramal, Navidea, Pfizer, Genzyme, Janssen AI, and Bristol-Myers-Squibb; no stock ownership, royalties, or patents.
Aisen	institutional research or clinical trial support (Lilly, >\$5K); consulting, advisory committee or speaker honoraria (none); no stock ownership, royalties, or patents.
Sperling	institutional research or clinical trial support (Lilly, >\$5K); consulting, advisory committee or speaker honoraria (none); no stock ownership, royalties, or patents.
Scheltens	institutional research or clinical trial support (GE Healthcare, >\$5K); consulting, advisory committee or speaker honoraria (Lilly, <\$5K); no stock ownership, royalties, or patents.
Fleisher:	institutional research or clinical trial support (Avid, >\$5K); consulting, advisory committee or speaker honoraria (<\$5K each: Avid, Lilly; honorarium from third party companies utilizing Lilly educational grant funding for educational programs related to amyloid imaging (non-promotional; >\$5K); no stock ownership, royalties, or patents.
Reiman	institutional research or clinical trial support (Avid, >\$5K); consulting, advisory committee or speaker honoraria (Bayer); no stock ownership, royalties, or patents.

Cummings	institutional research or clinical trial support (Avid, >\$5K); consulting, advisory committee or speaker honoraria (GE Healthcare); no stock ownership, royalties, or patents.
Weiner	institutional research or clinical trial support (>\$5K each: Merck, Avid); consulting, advisory committee or speaker honoraria (<\$5000 each: Pfizer, BOLT International, Janssen, KLJ Associates, Easton Associates, Harvard University, inThought INC Research, Inc., UCLA, Alzheimer's Drug Discovery Foundation, Sanofi-Aventis Groupe); stock ownership, royalties, or patents (Synarc, Elan).
Jagust	institutional research or clinical trial support (none); consulting, advisory committee or speaker honoraria (<\$5K each: Genentech, Synarc, Siemens, Janssen Alzheimer Immunotherapy, Sanofi); no stock ownership, royalties, or patents.
Relkin	None
Feldman	institutional research or clinical trial support (GEHC<\$5K, Lilly>\$5K); consulting, advisory committee or speaker honoraria (Institute for Clinical and Economic Review (ICER) Massachusetts General Hospital's Institute for Technology Assessment); no stock ownership, royalties, or patents.