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Office of Clinical Standards and Quality
Centers for Medicare & Medicaid Services
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Dear Dr. Jacques:

Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, is writing in follow-up to the January 30, 2012, meeting of the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) that focused on β-amyloid positron emission tomography (PET) imaging in dementia and neurodegenerative disease.

We strongly agree with the MEDCAC’s overall assessment that there is a lack of adequate evidence to determine whether PET imaging of brain β-amyloid changes the health outcomes (improved, equivalent, or worsened) 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 imaging of brain β-amyloid changes the health outcomes of any patient population. Therefore, we urge the Centers for Medicare & Medicaid Services (CMS) to maintain its current National Coverage Decision excluding coverage for such imaging.

In an editorial in the *European Journal of Nuclear Medicine and Molecular Imaging*, experts in the field of PET neuroimaging identified fundamental technological and practical problems with β-amyloid PET 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 β-amyloid 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, which are the gold standards for identifying β-amyloid deposits.

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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 contrast, autopsy studies of the brains of AD patients have demonstrated that the highest density of β-amyloid 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 β-amyloid plaques. Indeed, PET imaging with various purported amyloid agents consistently has shown higher ratios of white matter β-amyloid to grey matter β-amyloid 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 β-amyloid plaques and the small percentage of total brain area occupied by β-amyloid plaques even in the most severely affected cortical regions, amyloid agents such as florbetapir almost certainly do not have sufficiently greater uptake in β-amyloid deposits than in the background to allow accurate detection of β-amyloid 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. Such performance characteristics of β-amyloid PET 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 β-amyloid at subsequent autopsies (the gold standard for detecting brain β-amyloid) revealed significant variability among readers interpreting the PET scans. 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%

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percent, with a range of 69 to 92 percent, and the median specificity was 95 percent, with a range of 90 to 95 percent. 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 β-amyloid deposits — and no such test does exist — such imaging would still lack clinical utility because: (a) brain β-amyloid occur in multiple conditions, including normal aging; 5,6,7 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 β-amyloid.

In summary, we strongly recommend that CMS maintain its current National Coverage Decision excluding coverage for PET imaging of brain β-amyloid for the following major reasons:

1. There are no data from any completed, well-designed, controlled clinical trials evaluating whether PET imaging of brain β-amyloid 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 β-amyloid PET scans and those areas of the brain having the highest density of β-amyloid deposits at autopsy.
3. Interpretation of brain β-amyloid PET scans is subject to significant variability among readers.
4. The results of brain β-amyloid PET scans 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.

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Thank you for considering our comments regarding this important issue.

Sincerely,

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