EDITORIAL

Amyloid PET and Changes in Clinical Management for Patients With Cognitive Impairment

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In this issue of *JAMA*, Rabinovici and colleagues present the results of The Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) study.[1] The study had its origins in the 2013 decision by the US Centers for Medicare & Medicaid Services (CMS) that current evidence was insufficient to warrant coverage of amyloid positron emission tomography (PET) scanning for routine clinical care. However, in that decision, CMS agreed to provide coverage with evidence development in studies that would examine whether amyloid PET improved health outcomes in Medicare and Medicaid beneficiaries. Given that no disease-modifying treatments have yet been approved, health outcomes that can be assessed at this time are those related to diagnostic test ordering, symptomatic treatment decisions, or counseling, and these are the outcomes assessed in IDEAS.

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The study was designed with 2 primary aims. The first, which is reported in the article by Rabinovici et al, was to evaluate the association between amyloid PET and subsequent changes in clinical management. Importantly, the outcomes were actual rather than potential changes in care, ie, actions physicians took in response to PET findings. The study is ongoing, with the second aim focused on patient clinical outcomes, with results to be reported later. Although other studies have addressed these questions, IDEAS is by far the largest to date.

All participants in the IDEAS study were cognitively impaired, had either mild cognitive impairment (MCI) or dementia, and had to meet appropriate use criteria for amyloid PET that had been previously established by an expert panel commissioned by the Alzheimer's Association and the Society for Nuclear Medicine and Molecular Imaging.[2] The appropriate use criteria for amyloid PET are (1) an individual must have cognitive impairment for which the presumed etiology remained in question after an evaluation by a dementia specialist; (2) Alzheimer disease must be a diagnostic consideration; and (3) amyloid PET findings should reasonably be expected to change diagnosis and management. Diagnosis and management plans were documented before and 90 days after the amyloid PET scan in all participants.

The primary outcome assessed change in clinical management from the pre-PET to the post-PET visit, using a composite end point consisting of changes in prescription of Alzheimer disease drugs, prescription of non-Alzheimer disease drugs, or counseling about safety and future planning. Changes between the pre-PET and post-PET composite management end point occurred in 4159 of the 6905 patients with MCI (60%) and in 2859 of the 4504 patients with dementia (64%). This exceeded the prespecified target of 30% post-PET change in management. Moreover, physicians reported that PET results substantially influenced changes in clinical management 85% of the time when a change was made. For patients with MCI and dementia, respectively, the proportions with changes in each component of the outcome were 44% and 45% for changes in prescription of Alzheimer disease drugs, 23% and 25% for changes in prescription of non-Alzheimer disease drugs, and 24% and 21% for changes in counseling. This supports (but without randomization does not prove) a relationship between the PET findings and post-PET changes in management.

This study has several notable aspects. The large numbers of participants enrolled (16 008 registered and 11 409 completed), the large number of participating physicians (946) and sites (595), and the rapid enrollment of such a large number of participants (19 months) all reflect the enthusiasm of both patients and dementia specialists for clinical application of amyloid PET imaging. This could be interpreted as evidence of pent-up clinical demand. Also, the median age of participants (75 years for patients with MCI and 77 years for those with dementia) was slightly older than the age of those who typically participate in clinical trials. Thus, this cohort more closely reflects the age when cognitive impairment becomes a major public health problem.

An important finding was the discrepancy between presumed etiology underlying impairment based on standard of care clinical assessments pre-PET, and the etiology as informed by amyloid PET. Amyloid PET results were negative in 3175 of 8770 patients (36%) in whom Alzheimer disease was considered pre-PET to be a major contributing etiology. Given that both amyloid-β and pathologic tau deposits are required for a neuropathologic diagnosis of Alzheimer disease[3] (the accepted gold standard), this means that a presumed etiology of Alzheimer disease based on clinical assessment by dementia experts was incorrect for approximately one-third of patients. This result is consistent with prior evidence.[4-6] Conversely, amyloid PET results were positive in 1378 of 2639 patients (52%) with a pre-PET presumed non-Alzheimer disease etiology. These data highlight the disconnect between presumed etiology of impairment based on syndromic presentation alone and the underlying biology based on biomarker or neuropathologic evidence and has important implications for future clinical trials.[4-6]

Based on criteria that have been in clinical use for 35 years,[7,8] the diagnosis of probable or possible Alzheimer

disease has been made on clinical grounds after other possible causes are excluded. The classic syndromic presentation of probable Alzheimer disease is a progressive amnestic, multidomain dementia. It is a clinical-pathologic construct, in that possible and probable Alzheimer disease diagnoses can be made during a patient's life but definite Alzheimer disease can only be diagnosed at autopsy.[7,8] Often, however, this critical distinction between probable diagnosis and definitive diagnosis is neglected, and patients are simply given a diagnosis of Alzheimer disease based on clinical presentation alone.[9] However, the neuropathology of brain aging is heterogeneous and the amnestic syndromic presentation classically associated with Alzheimer disease can also be associated with other common neuropathologic disorders; among these are cerebrovascular disease and TDP43 proteinopathy with or without hippocampal sclerosis, α-synuclein, and argyrophillic grains.[10-12]

Thus, a clinical diagnosis of probable Alzheimer disease does not guarantee that Alzheimer disease is the major etiology underlying symptoms; nor does the absence of an amnestic presentation guarantee that Alzheimer disease is not the major etiology underlying symptoms. Moreover, most often, multiple neuropathologic disorders are found in cognitively impaired individuals at autopsy, and this trend becomes more pronounced with advancing age.[13,14] Hence, a cautionary note is that physicians should remain alert for additional contributing disease processes, even after a positive amyloid PET scan result is obtained. The major neuropathology underlying a diagnosis of MCI is Alzheimer disease in about 55% to 60% of cases[15]; thus, even greater etiologic uncertainty is associated with this syndrome in comparison to a clinical diagnosis of probable Alzheimer disease.

An important caveat when discussing etiology in the context of the IDEAS study is that amyloid PET detects only 1 of the 2 hallmark proteinopathies (amyloid deposition and tau deposition) necessary to diagnose Alzheimer disease[3]. Thus, a positive amyloid PET result alone is not completely diagnostic of Alzheimer disease; it only indicates that the patient is within the Alzheimer continuum,[16] because an abnormal tau biomarker is needed as well to identify Alzheimer disease in vivo. However, an abnormal amyloid PET scan result greatly increases the likelihood that Alzheimer disease is present.[17] The IDEAS study represents an important first step in delineating the total biomarker profile for a cognitively impaired individual.[12]

Although the findings of the IDEAS study show that improved knowledge about etiology provided by amyloid PET, over and above current standards of clinical care, changes clinical management, there are important nuances to this broad conclusion. Presumed etiology, not just clinical symptoms, is important to management. The nature of management changes from pre- to post-PET show that physician management is largely driven by expected etiology. The most frequent change in management involved the use of Alzheimer disease drugs, the aspect of management most directly linked with presumed etiology. However, additional information is needed from the ongoing clinical outcomes component of the study. For CMS to cover the cost of amyloid PET, it must be demonstrated that the result of a scan has an effect on patient outcomes, not just patient care processes—and, without a disease-modifying therapy available, that might be a challenge.

As acknowledged by the authors, a disappointing feature of the study was the low participation rate by nonwhite patients. This reflects a challenge that limits the generalizability of the findings. Clearly, the field needs to embrace this challenge, and CMS would likely be more favorable toward providing coverage if data were available from a more representative sampling of the population.

The IDEAS study followed appropriate use criteria for amyloid PET in that etiologic uncertainty must have been present for inclusion.[2] However, even among patients who meet classic clinical criteria for probable Alzheimer disease where etiologic certainty is greater, considerable diagnostic inaccuracy exits. In recently completed Alzheimer disease clinical trials, approximately 35% of apolipoprotein E ε4 (*APOE*E4*) noncarriers who met classic criteria for probable Alzheimer disease had negative amyloid PET scan results.[5,6] This begs the question, should appropriate use criteria for amyloid PET be expanded to include probable Alzheimer disease? Conversely, only 7% of *APOE*E4* carriers in these trials had negative amyloid PET scan results.[5,6] This raises a related question, should genetic testing (*APOE*) be used for triage in patients who unequivocally meet criteria for probable Alzheimer disease—ie, amyloid PET for *APOE*E4* noncarriers but not for carriers?

Given the evidence provided by the IDEAS study that more specific knowledge provided by biomarkers about etiology of impairment was associated with changes in short-term clinical management, a path forward seems apparent. More detailed etiologic characterization by deeper biomarker-based phenotyping will result in more precise, patient-specific management decision making. Ultimately, the hope is that management will include access to pathophysiologically appropriate, disease-modifying interventions.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: Dr Jack reported that he consults for Lilly and serves on an independent data monitoring board for Roche but receives no personal compensation from any commercial entity and that he receives research support from the National Institutes of Health and the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Clinic. Dr Petersen reported receiving personal fees from Hoffman-La Roche, Merck, Genentech, Biogen, GE Healthcare, and Eisai.

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