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# Assessment of the Incremental Diagnostic Value of Florbetapir F 18 Imaging in Patients With Cognitive Impairment

## The Incremental Diagnostic Value of Amyloid PET With [$^{18}$F]-Florbetapir (INDIA-FBP) Study

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**IMPORTANCE** Cerebral amyloidosis is a key abnormality in Alzheimer disease (AD) and can be detected in vivo with positron emission tomography (PET) ligands. Although amyloid PET has clearly demonstrated analytical validity, its clinical utility is debated.

**OBJECTIVE** To evaluate the incremental diagnostic value of amyloid PET with florbetapir F 18 in addition to the routine clinical diagnostic assessment of patients evaluated for cognitive impairment.

**DESIGN, SETTING, AND PARTICIPANTS** The Incremental Diagnostic Value of Amyloid PET With [$^{18}$F]-Florbetapir (INDIA-FBP) Study is a multicenter study involving 18 AD evaluation units from eastern Lombardy, Northern Italy, 228 consecutive adults with cognitive impairment were evaluated for AD and other causes of cognitive decline, with a prescan diagnostic confidence of AD between 15% and 85%. Participants underwent routine clinical and instrumental diagnostic assessment. A prescan diagnosis was made, diagnostic confidence was estimated, and drug treatment was provided. At the time of this workup, an amyloid PET/computed tomographic scan was performed, and the result was communicated to physicians after workup completion. Physicians were asked to review the diagnosis, diagnostic confidence, and treatment after the scan. The study was conducted from August 5, 2013, to December 31, 2014.

**MAIN OUTCOMES AND MEASURES** Primary outcomes were prescan to postscan changes of diagnosis, diagnostic confidence, and treatment.

**RESULTS** Of the 228 participants, 107 (46%) were male; mean (SD) age was 70.5 (7) years. Diagnostic change occurred in 46 patients (79%) having both a previous diagnosis of AD and an amyloid-negative scan ($P < .001$) and in 16 (53%) of those with non-AD diagnoses and an amyloid-positive scan ($P < .001$). Diagnostic confidence in AD diagnosis increased by 15.2% in amyloid-positive ($P < .001$; effect size Cohen $d = 1.04$) and decreased by 29.9% in amyloid-negative ($P < .001$; $d = -1.19$) scans. Acetylcholinesterase inhibitors and memantine hydrochloride were introduced in 61 (65.6%) patients with positive scan results who had not previously received those drugs, and the use of the drugs was discontinued in 6 (33.3%) patients with negative scan results who were receiving those drugs ($P < .001$).

**CONCLUSIONS AND RELEVANCE** Amyloid PET in addition to routine assessment in patients with cognitive impairment has a significant effect on diagnosis, diagnostic confidence, and drug treatment. The effect on health outcomes, such as morbidity and mortality, remains to be assessed.

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Supplemental content

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Brain β-amyloid is a hallmark of Alzheimer disease (AD)[1-3] and is quantifiable in vivo through specific positron emission tomography (PET) radiotracers binding to β-amyloid with 96% to 97.8% sensitivity and 88.9% to 100% specificity.[4,5]The F 18–labeled tracers (eg, [$^{18}$F]-florbetapir, [$^{18}$F]-flutemetamol, and [$^{18}$F]-florbetaben) now overcome the limited clinical applicability of carbon 11–labeled Pittsburgh Compound B[6] with their longer half-life (110 minutes). This evidence of analytical validity and feasibility makes amyloid PET a promising pathophysiologic marker for diagnosing AD according to most recent criteria.[7-9] However, the clinical utility of amyloid PET is still under investigation worldwide. The presence of brain amyloidosis in patients with clinically diagnosed AD or lack thereof in individuals without AD is not warranted. In a recent meta-analysis,[10] the prevalence of positive scans was 88% in patients with AD, 51% in patients with dementia with Lewy bodies (DLB), 30% in those with cerebrovascular disease (CVD), 12% in patients with frontotemporal lobar degeneration (FTLD), 38% in those with corticobasal degeneration (CBD), and 24% in healthy elderly individuals serving as controls. Consequently, amyloid PET, although approved for clinical use, is still not reimbursed by national health care systems. In the United States, a wide collection of clinical cases using amyloid PET, funded by private and public sources,[11] perform amyloid PET scans in cases consistent with the pertinent Appropriate Use Criteria,[12,13] collecting quantitative evidence on the incremental value of the examination for a large sample. To date, the published evidence on the added value of amyloid PET has important limitations.

The aim of this study was to quantify the effect of amyloid PET on the routine clinical diagnostic assessment of a large set of patients evaluated for cognitive impairment in a naturalistic setting. At variance with the largest study published so far[14] and similar to only preliminary evidence,[15-20] in our study the clinicians relied on amyloid PET for their final clinical diagnoses and identification of the most appropriate treatment.

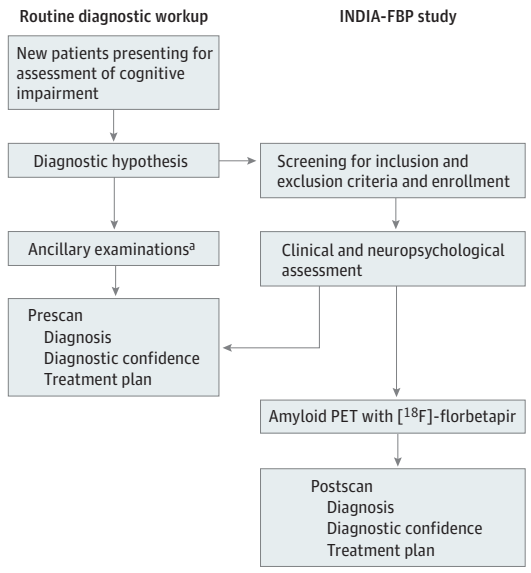
### Key Points

**Question** Is amyloid positron emission tomography (PET) scanning useful for the assessment of patients with cognitive impairment?

**Findings** In this multicenter study of 228 cognitively impaired adults undergoing amyloid PET, results inconsistent with previous diagnosis led to significant changes in diagnosis, diagnostic confidence, and therapeutic plan.

**Meaning** Amyloid PET has a significant effect on the evaluation of patients for cognitive impairment.

Figure 1. Study Design




Patients enrolled in this study were outpatients seeking evaluation in 18 Alzheimer disease evaluation units. They received their routine diagnostic workup as defined by the local dementia expert. Based on clinical features, patients were screened for eligibility for the Incremental Diagnostic Value of Amyloid PET With [$^{18}$F]-Florbetapir study (INDIA-FBP). Those who were enrolled underwent a standardized neuropsychological battery that was included in the local routine diagnostic workup. Local dementia experts then formulated prescan and postscan diagnosis, diagnostic confidence, and treatment plan.

[a] The prescan workup could include magnetic resonance imaging, computed tomography, fludeoxyglucose F 18 positron emission tomography, cerebrospinal fluid collection, and clinical and neuropsychological assessment.

## Methods

### Study Design

The Incremental Diagnostic Value of Amyloid PET With [$^{18}$F]-Florbetapir (INDIA-FBP) Study is an open-label, multicenter study in which patients were evaluated and underwent instrumental examination as routinely required in 18 AD evaluation units from eastern Lombardy, Northern Italy (EudraCT 2012-003079-20). Most patients receiving care at memory clinics have cognitive symptoms and are referred by general practitioners. The coordinating centers, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy, and Azienda Socio Sanitaria Territoriale of Spedali Civili, Brescia, Italy, contributed patients from their internal memory clinics with the same procedure as the other memory clinics. The study was performed as illustrated in **Figure 1**. The study was approved by the local ethics committee (Comitato Etico delle Istituzioni Ospedaliere) and adhered to the Declaration of Helsinki.[21] All participants or their representatives provided written informed consent before entering the study. Participants did not receive financial compensation. The study was conducted from August 5, 2013, to December 31, 2014.

During the first visit, the dementia expert (a neurologist or geriatrician) performed a cognitive, physical, and neurologic examination and made a preliminary evaluation of eligibility. Enrolled patients underwent the local routine diagnostic workup and ancillary examinations (eg, magnetic resonance imaging, computed tomography (CT), $^{18}$F-fludeoxyglucose-PET/CT, cerebrospinal fluid collection, and clinical and neuropsychological assessment), except amyloid PET, which is usually performed to achieve the

final formulation of diagnosis and treatment plan in Italian memory clinics. Patients also underwent a standard clinical and neuropsychological assessment specific to this study (eMethods in the Supplement). The assessment includes 2 tests evaluating the global cognition: Mini-Mental State Examination (range: 0 [worse performance] to 30 [better performance])[22] and Alzheimer's Disease Assessment Scale-Cognitive subscale (range 0 [better performance] to 70 [worse performance]).[23]

When the local routine diagnostic workup was completed, physicians formulated their diagnosis, rated their confidence that cognitive impairment was due to AD on a scale of 0% to 100%, and prescribed drug treatment based on the workup (prescan assessment). Between the first visit and prescription of drug treatment, patients underwent the amyloid PET/CT; the results were communicated to physicians only after the workup was completed and the prescan assessment was formulated. After disclosure of the amyloid PET result, dementia experts were asked to revise patients' diagnosis, diagnostic confidence, and drug treatment (postscan assessment). Thus, any changes before and after the scan can only be attributed to knowing such results.

## Participants

Participants were consecutive patients receiving care at AD evaluation units for diagnosis of cognitive abnormalities and suspicion of AD. Inclusion criteria were cognitive abnormality, age between 50 and 85 years, availability of an informant (spouse, adult child, or other knowledgeable informant), and a prescan diagnostic confidence of AD between 15% and 85%. Exclusion criteria were having a score greater than 2 on the Clinical Dementia Rating scale at baseline (range, 0-3)[24]; having clinically significant psychiatric conditions potentially preventing a PET scan; being a woman with childbearing potential unless receiving contraceptives; having a relevant history of severe drug allergy or hypersensitivity; previous participation in an experimental study using an amyloid-targeting agent, unless documented that the participant had received only placebo during the whole time of the study; receipt of investigational medications within the past 30 days; and having had radiopharmaceutical imaging or treatment within 7 days before the study imaging session. Based on an estimate from the 4 top-recruiting centers (amyloid PET requests on total number of new patients in the enrolling period), these criteria select 14% to 27% of new patients referred to Northern Italy memory clinics.

## Outcome Variables

Outcome variables of this study were diagnosis, diagnostic confidence, and treatment plan. Throughout the study, dementia experts evaluated patients 3 times (Figure 1). The first time corresponded to the first visit. At time 2, diagnosis, diagnostic confidence, and treatment plan were based on clinical evaluation and ancillary examinations. At time 3, physicians received the amyloid PET result and reformulated the diagnosis, diagnostic confidence, and treatment plan based on the amyloid PET result. At each evaluation physicians uploaded information using a shared web portal.[25]

### Diagnosis and Diagnostic Confidence

At the beginning of the study, the project principal investigators and the study management team organized an in-person meeting with participating physicians from the memory clinics who were briefed on the latest scientific literature on amyloid imaging in humans and diagnostic criteria for AD and non-AD conditions (eMethods in the Supplement). At each time point of the study, physicians were asked to stage cognitive impairment (ie, mild cognitive impairment or dementia), express an etiologic diagnosis, and rate their diagnostic confidence (0%-100%) that the cognitive impairment was consistent with an AD etiology. Etiologic diagnoses were AD (eg, typical or atypical AD, mixed AD, or AD with comorbidity) or non-AD. The non-AD diagnoses were further grouped into FTLD and subcortical diseases (ie, CVD, DLB, CBD, Parkinson disease dementia, multiple system atrophy, progressive supranuclear palsy, and normal pressure hydrocephalus).

### Treatment Plan

At all time points, physicians reported medication prescription as follows: (1) acetylcholinesterase inhibitors; (2) memantine hydrochloride; (3) anxiolytics, hypnotics, or antidepressants; and (4) antipsychotics or anticonvulsants. These drugs were further grouped as cognition specific (ie, acetylcholinesterase inhibitors and memantine) and non-cognition specific (ie, anxiolytics, hypnotics, antidepressants, antipsychotics, and anticonvulsants).

## Amyloid PET Imaging

PET/CT scans with [$^{18}$F]-florbetapir were acquired at Poliambulanza Foundation (Siemens Biograph 40 mCT; Siemens Healthineers) and at Azienda Socio Sanitaria Territoriale of Spedali Civili, Brescia, Italy (GE Discovery 690; GE Healthcare). A total of 370 MBq (10 mCi) of [$^{18}$F]-florbetapir was injected as an intravenous bolus, and acquisition and reconstruction followed standard operating procedures.[26] One nuclear medicine physician per center (U.P.G. and B.P.) was trained to visually read scans and rate them as amyloid positive or amyloid negative following the procedures provided by the ligand manufacturer. Visual reading was performed independently by both readers for all scans, blinded to patients' diagnosis and clinical information. Throughout the study, the readers evaluated visually, with a dichotomous output (positive or negative), 267 amyloid PET scans (including 241 patients and 26 healthy elderly controls). The readers had a concordance rate of 87% (Cohen $\kappa$ = 0.74; SE, 0.042, indicating very good agreement), disagreeing in 34 cases, on the first round. The agreement converged over a second round of joint reading in 19 (56%) of these cases. The remaining 15 cases were read by a reference expert from the ligand manufacturer (Avid Radiopharmaceuticals).

The 26 persons serving as controls were cognitively intact and between ages 52 and 79 years. Those with amyloid-positive scan results were 4 persons aged 60, 66, 70, and 71 years (15% of the controls).

## Statistical Analysis

For each diagnosis we pooled patients with mild cognitive impairment and those with dementia. We assessed normal-

Table. Demographic and Clinical Characteristics of the 228 Participants Based on Prescan Diagnosis

| Characteristic | AD (n = 165) | Non-AD (n = 63) | *P* Value[a] | Non-AD (n = 63) | |
|---|---|---|---|---|---|
| | | | | FTLD (n = 37) | Subcortical Diseases (n = 26)[b] |
| Age, mean (SD), y | 70.9 (6.8) | 69.4 (7.4) | .21 | 68.6 (7.9) | 70.7 (6.6) |
| Male, No. (%) | 75 (45.5) | 32 (50.8) | .57 | 19 (51.4) | 13 (50) |
| Mild cognitive impairment, No. (%) | 90 (54.5) | 20 (31.7) | .003 | 12 (32.4) | 8 (30.8) |
| Diagnostic confidence, % (SD)[c] | 71 (12) | 30 (10) | <.001 | 32 (10) | 27 (9) |
| Education, mean (SD), y | 9.0 (4.3) | 8.7 (4.4) | .46 | 9.3 (4.1) | 7.9 (4.6) |
| MMSE score, mean (SD)[d] | 23.1 (4.2) | 22.4 (5.2)[e] | .48 | 22.4 (5.2)[e] | 22.3 (5.3) |
| ADAS-COG subscale score, mean (SD)[f] | 17.7 (8.6) | 19.6 (11.0)[e] | .56 | 19.9 (11.3)[e] | 19.2 (10.8) |

Abbreviations: ADAS-COG, Alzheimer's Disease Assessment Scale–Cognitive; FTLD, frontotemporal lobar degeneration; MMSE, Mini-Mental State Examination.

[a] Significance determined using Mann-Whitney or $\chi^2$ tests.

[b] Cerebrovascular disease, 11 patients; dementia with Lewy bodies, 5; corticobasal degeneration, 4; Parkinson disease dementia, 3; multiple system atrophy, 1; progressive supranuclear palsy, 1; and normal pressure hydrocephalus, 1.

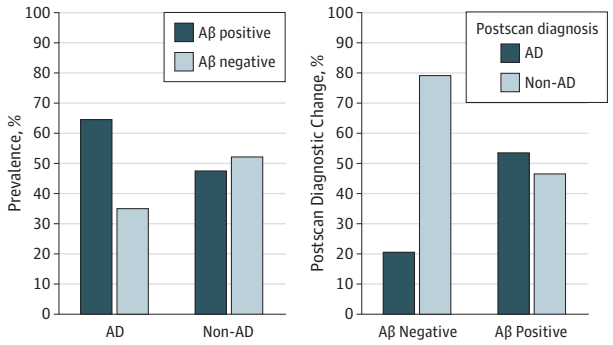
[c] The level of confidence that cognitive impairment is due to AD, thus, differing by definition among groups.

[d] The MMSE is scored from 0 (worse performance) to 30 (better performance).

[e] One patient with FTLD refused neuropsychological evaluation.

[f] The ADAS-COG subscale is scored from 0 (better performance) to 70 (worse performance).

Figure 2. Amyloid Positron Emission Tomography Result and Diagnostic Change by Prescan Diagnosis




Postscan diagnostic changes occurred only in the Alzheimer disease (AD)-negative and in non-AD–positive groups.

ity of data distribution through histogram inspection and the Shapiro-Wilk normality test. Because of nonnormal distribution of data, we performed nonparametric analyses (Mann-Whitney test and Wilcoxon signed rank test). For categorical variables, the $\chi^2$ test (or Fisher exact test for small samples) was used. Effect size metrics were computed with Cohen *d* for continuous variables (0.20 [small], 0.50 [moderate], and 0.80 [large] effect sizes), or Φ for categorical variables (0.10 [small], 0.30 [moderate], and 0.50 [large] effect sizes). The 1-sample proportions test was used to evaluate whether proportions of patients showing changes owing to amyloid PET are significantly different from 0.00001 (ie, virtually no change expected in the absence of amyloid PET). We assessed interrater agreement for amyloid PET scan visual reading between the 2 nuclear medicine physicians with the Cohen κ coefficient (0.20 [fair], 0.40 [moderate], 0.60 [good], and 0.80 [very good] strength of agreement) and the rate of concordance. All statistical analyses were performed with R, version 3.1.1 (R Foundation for Statistical Computing, https://www.r-project.org/).

## Results

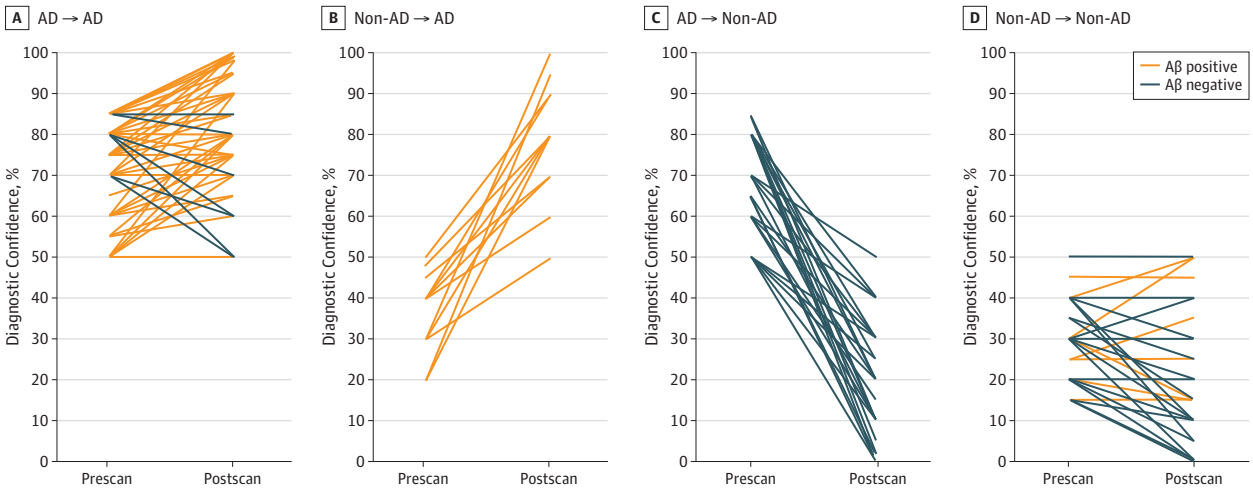
### Prescan Demographics, Diagnosis, and Diagnostic Confidence

Of the 241 enrolled patients, 2 individuals were excluded owing to incomplete data and 11 were excluded because of prescan diagnostic confidence for AD of less than 15% or more than 85%; 228 patients were included in the analyses. Mean (SD) age was 70.5 (7) years. Clinical and sociodemographic features between patients initially diagnosed as having AD or non-AD were similar, with the exception of the prevalence of mild cognitive impairment syndrome, which was more frequent in patients with AD ($\chi^2$ = 8.60, *P* = .003, Φ = 0.20). By definition, non-AD cases had lower diagnostic confidence than AD cases (Mann-Whitney, 10 356, *P* < .001, Cohen *d* = 3.69) (**Table**). Of the patients who had a prescan diagnosis other than AD, 37 had a diagnosis of FTLD and 26 had a diagnosis of subcortical diseases (CVD, 11; DLB, 5; CBD, 4; Parkinson disease dementia, 3; multiple system atrophy, 1; progressive supranuclear palsy, 1; and normal pressure hydrocephalus, 1). Diagnoses were equally represented among patients recruited by academic and nonacademic memory clinics. Moreover, the consensual reading used in this study led to the same results as single-rater visual reading.

### Prevalence of Positive Amyloid PET Scan Results

The prevalence of positive scan results was greater for patients with a prescan diagnosis of AD than for those with non-AD diagnoses ($\chi^2$ = 4.95, *P* = .03, Φ = 0.16), but the latter was not negligible (**Figure 2**). A similar prevalence of positivity was found in the FTLD group (18 of 37 [48.6%]) and subcortical group (12 of 26 [46.2%]) ($\chi^2$ = 0, *P* > .99, Φ = 0.02).

Figure 3. Changes in the Confidence That Cognitive Impairment in the Patients Is Attributable to Alzheimer Disease (AD)




The diagnostic confidence that cognitive impairment was due to AD increased for patients with a confirmed diagnosis of AD (Δ = 10.7%; SD, 11.8%) (A) and for patients whose diagnosis changed from non-AD to AD (Δ = 43.2%; SD, 16.2%) (B). Consistently, diagnostic confidence decreased in patients whose diagnosis changed from AD to non-AD (Δ = 48.7%; 17%) (C) and in patients with confirmed diagnosis of non-AD (Δ = 7.9%; SD, 11.9%) (D). All changes were significant at $P < .001$.

### Effect of Amyloid PET on Diagnosis

As expected, the negative predictive value of amyloid scans had a greater effect on diagnostic change of patients with AD than on the positive predictive value in those without AD (46 [79%] vs 16 [53%]; $\chi^2 = 5.22$, $P = .02$, $\Phi = 0.27$) (Figure 2).

Among clinically diagnosed non-AD disorders, amyloid PET more frequently helped in the diagnosis of patients with an FTLD syndrome (change observed in 72% of patients with FTLD and positive scan results) than that of patients with subcortical disease (change observed in 25% patients with positive scan results); the difference was significant ($\chi^2 = 4.69$, $P = .02$, $\Phi = 0.46$). When patients with FTLD had a diagnostic change resulting from a positive scan, this led invariably to an AD diagnosis. However, when the change was observed in patients diagnosed with AD before the scan, greater variability of the final diagnoses occurred in those with a negative scan result (eTable 1 in the Supplement). Overall, 123 of 137 patients (89.8%) with amyloid-positive results received a final diagnosis of AD, and 79 of 91 (86.8%) of those with amyloid-negative results received a final diagnosis of non-AD.

### Effect of Amyloid PET on Diagnostic Confidence

The availability of amyloid imaging positively affected diagnostic confidence both after positive (Δ = 15.2; SD, 15; Wilcoxon signed rank, 165; $P < .001$; Cohen $d = 1.04$) and negative (Δ = −29.9; SD, 24.1; Wilcoxon signed rank, 2972.5; $P < .001$; Cohen $d = -1.19$) scan results and for AD and non-AD diagnoses (**Figure 3**). The greater or negative Δ values depicted in Figure 3B and C reflect diagnostic changes, with the figure representing confidence that cognitive impairment is due to AD. Significant increases in diagnostic confidence were also observed when the diagnosis did not change from before the scan to after the scan (Figure 3A and D) ($P < .001$ for both AD and non-AD diagnoses). Patients with a confirmed diagnosis of AD despite negative scan results had greater prescan diagnostic confidence than did patients with AD who had negative results and had their diagnosis changed (75.8% vs 67.9% respectively; Wilcoxon signed rank, 376.5; $P < .05$; Cohen $d = 0.63$).

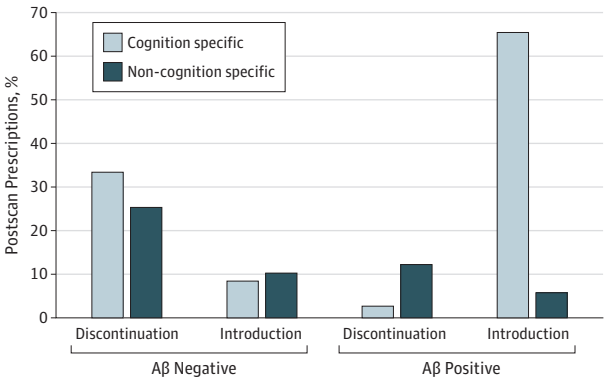
### Influence of Amyloid PET on Treatment Plans

A relevant influence of amyloid PET was observed for treatment plans. A positive amyloid PET scan result led to introduction of cognition-specific medications in 61 (65.6%) of previously untreated patients, and negative results led to drug discontinuation in 6 (33.3%) of previously treated patients ($P < .001$) (**Figure 4**).

## Discussion

In this study, we estimated the incremental value of amyloid PET when added to the routine diagnostic procedures of largely nonacademic Italian AD evaluation units in eastern Lombardy. The population from which patients were recruited is representative of the Northern Italian population seeking specialist help for cognitive impairment. This kind of study is key to the assessment of the clinical utility of amyloid PET as an AD biomarker. We found significant changes in diagnosis, diagnostic confidence, and treatment for patients with amyloid-positive as well as those with amyloid-negative results. Changes were within the range of available evidence to date (eTable 2 in the Supplement). However, different from the largest study[14] published so far in which the effect of intended use of amyloid PET was estimated retrospectively, in the present study, amyloid PET results were used for the definition of the final diagnosis and patient treatment plan, and our results provide a realistic estimate of the incremental value of the examina-

Figure 4. Cognition-Specific and Non–Cognition-Specific Medication Prescriptions After Amyloid Positron Emission Tomography (PET)




Prescriptions for cognition-specific medications (acetylcholinesterase inhibitors and memantine hydrochloride) and non–cognition-specific medications (anxiolytics, hypnotics, antidepressants, antipsychotics, and anticonvulsants) that were introduced after amyloid PET in patients who were previously not receiving the same medication or discontinued after amyloid PET in patients who were previously receiving it. All changes were significant at $P < .001$ in a 1-sample proportions test.

tion in routine clinical settings. This design qualifies it as a phase 4 study according to a 5-phase biomarker validation framework recently adapted to the AD field.[27]

Among patients who had AD diagnosed before amyloid PET scans were performed, as many as 58 (35%) had a negative scan. This percentage is within the range reported by clinical studies (12%-38%)[14-18,28-30] (eTable 2 in the Supplement) and slightly higher than the percentage of patients with AD who had no more than sparse neuritic amyloid plaques at autopsy (14%-25%).[31,32] Among patients with a clinical non-AD diagnosis, as many as 48% had a positive scan result. This finding is consistent with the range of 12% to 51% positivity reported for non-AD diagnoses, such as DLB, CBD, CVD, and FTLD,[10] as well as within the range observed for the previously available studies[14-18,28-30] on the incremental value of amyloid imaging (eTable 2 in the Supplement).

Inconsistent scan results led to diagnostic changes in a relevant proportion of cases: 46 (79%) of patients with clinically diagnosed AD with negative amyloid PET scan results had their diagnosis changed to non-AD diseases, confirming the important negative predictive value of amyloid imaging (Figure 2). Twelve patients, however, had their AD diagnosis confirmed. These 12 patients had a higher diagnostic confidence for AD before the amyloid PET scan than did patients with AD with a revised diagnosis, suggesting a more prototypical AD clinical picture. The fact that their diagnosis was not changed to suspected non-AD pathology (SNAP) may suggest that SNAP is not yet recognized as a clinical entity despite data suggesting slower progression than with amyloid-positive AD.[33] We should, however, consider that the sensitivity of [$^{18}$F]-florbetapir in detecting brain amyloidosis is 92%[4]; thus, 12 patients with false-negative scan results can be expected in our sample.

Among patients with a previous diagnosis of AD and negative amyloid scan, a comparable proportion in the present study and in a previous study[20] (19% and 23.5%, respectively) had their diagnosis changed to FTLD. The other most common diagnosis in our sample was cognitive impairment due to CVD and as noted in depression; Rabinovici et al[20] observed a larger amount of CBD after negative scans, which was possibly explained by more cases of rare dementia in his level III memory clinic.

Fourteen patients (47%) without AD did not have their diagnosis changed despite positive scan results, which is consistent with the known prevalence of brain amyloidosis in neurodegenerative diseases other than AD and with age-related asymptomatic brain amyloidosis in normal aging.[10,34] This finding also denotes that physicians use the positive predictive value of amyloid imaging in their diagnostic procedure, although its negative predictive value is considered the strongest source of added value.

As described above, inconsistent amyloid PET scans led to diagnostic changes in most patients. However, amyloid PET also showed clinical utility for cases with confirmed diagnoses, significantly increasing the diagnostic confidence that cognitive impairment was due to AD for confirmed AD cases and reducing such confidence for confirmed non-AD cases.

The treatment plan was also changed following amyloid PET scans, which was consistent with scan results and diagnostic changes. Although the current impact of amyloid PET is debatable owing to a lack of disease-modifying drugs, future therapies may need to leverage on amyloid PET results. At present, more accurate etiologic diagnosis and targeted drug treatment are justified by reports of adverse events in patients with FTLD treated with cholinesterase inhibitors[35-37] and of ineffectiveness for cognitive impairment of vascular etiology.[38] Additional advantages of this expensive examination consist of the formulation of a benign diagnosis in patients with mild cognitive impairment who have negative scan results, and undergoing such an examination provides more certain answers to patients with positive scans who require diagnosis. In these cases, earlier intervention can be started.[39] Recruitment in clinical trials and the possibility for patients and caregivers to make residence and financial arrangements at a time when patients are still able to express their preference may be considered when weighing costs and benefits. The rapid evolution of biomarkers[40] and treatment requires periodic revisions of the cost-benefit ratio.

## Limitations

Although the multicenter design can be considered a strength of this study, this is also the source of its limitations since patients did not follow a fully standardized procedure for their diagnostic assessment. The incremental value of amyloid PET may differ depending on the set of instrumental investigations conducted before the scan, which is an issue that warrants further investigation.

Physicians' backgrounds may also have an effect in the study. In Italy, patients with cognitive impairment who present to memory clinics are assessed by neurologists or geriatricians who see patients with AD or related disorders for all or most of their working time.[41] These experts have a similar background regarding the specificity of the examined disorders, and we provided a common background on all participants at the beginning of this study. However, differences among professional specialization, continuing medical edu-

cation, or other variables, such as beliefs on the role of amyloid in AD pathogenesis,[42] may affect the use of amyloid PET results and were not controlled for in this study.

## Conclusions

We have shown an effect of amyloid PET scans on diagnostic thinking and patient management when used in addition to routine diagnostic workup. Studies ongoing in the United States and Europe (Imaging Dementia—Evidence for Amyloid Scanning[11] and Amyloid Imaging to Prevent Alzheimer's Disease[43]) are expanding these observations on a larger scale and launching health technology assessments that will quantify cost-effectiveness of amyloid PET in clinical routine. Future efforts will need to focus on direct comparisons of amyloid PET with other (most importantly, cerebrospinal fluid) biomarkers with the aim of defining diagnostic algorithms and guidelines.

ARTICLE INFORMATION

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**Author Contributions:** Dr Boccardi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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## REFERENCES


1. Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science*. 1992;256(5054):184-185.

2. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*. 2002;297(5580):353-356.

3. Karran E, Mercken M, De Strooper B. The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. *Nat Rev Drug Discov*. 2011;10(9):698-712.

4. Clark CM, Pontecorvo MJ, Beach TG, et al; AV-45-A16 Study Group. Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-β plaques: a prospective cohort study. *Lancet Neurol*. 2012;11(8):669-678.

5. Sabri O, Sabbagh MN, Seibyl J, et al; Florbetaben Phase 3 Study Group. Florbetaben PET imaging to detect amyloid beta plaques in Alzheimer's disease: phase 3 study. *Alzheimers Dement*. 2015;11(8):964-974.

6. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol*. 2004;55(3):306-319.

7. Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol*. 2014;13(6):614-629.

8. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):270-279.

9. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):263-269.

10. Ossenkoppele R, Jansen WJ, Rabinovici GD, et al; Amyloid PET Study Group. Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. *JAMA*. 2015;313(19):1939-1949.

11. IDEAS. Imaging Dementia—Evidence for Amyloid Scanning study. http://www.ideas-study.org/. Accessed July 28, 2016.

12. Johnson KA, Minoshima S, Bohnen NI, et al; Alzheimer's Association; Society of Nuclear Medicine and Molecular Imaging; Amyloid Imaging Taskforce. 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. *Alzheimers Dement*. 2013;9(1):e-1-e-16.

13. Johnson KA, Minoshima S, Bohnen NI, et al. Update on Appropriate Use Criteria for amyloid PET imaging: dementia experts, mild cognitive impairment, and education. *J Nucl Med*. 2013;54(7):1011-1013.

14. Grundman M, Pontecorvo MJ, Salloway SP, et al; 45-A17 Study Group. Potential impact of amyloid imaging on diagnosis and intended management in patients with progressive cognitive decline. *Alzheimer Dis Assoc Disord*. 2013;27(1):4-15.

15. Zwan MD, Bouwman FH, Van der Flier WM, Lammertsma A, Van Berckel B, Scheltens P. Diagnostic value of amyloid imaging in early onset dementia [abstract IC-P-013]. *Alzheimers Dement*. 2014;10(4)(suppl):14. doi:10.1016/j.jalz.2014.05.017

16. Jiménez-Bonilla JF, Banzo I, De Arcocha-Torres M, et al. Amyloid imaging with 11C-PIB in patients with cognitive impairment in a clinical setting: a visual and semiquantitative analysis. *Clin Nucl Med*. 2016;41(1):e18-e23.

17. Frederiksen KS, Hasselbalch SG, Hejl AM, Law I, Højgaard L, Waldemar G. Added diagnostic value of (11)C-PiB-PET in memory clinic patients with uncertain diagnosis. *Dement Geriatr Cogn Dis Extra*. 2012;2(1):610-621.

18. Zannas AS, Doraiswamy PM, Shpanskaya KS, et al. Impact of $^{18}$F-florbetapir PET imaging of β-amyloid neuritic plaque density on clinical decision-making. *Neurocase*. 2014;20(4):466-473.

19. Mitsis EM, Bender HA, Kostakoglu L, et al. A consecutive case series experience with [$^{18}$F] florbetapir PET imaging in an urban dementia center: impact on quality of life, decision making, and disposition. *Mol Neurodegener*. 2014;9:10.

20. Rabinovici GD, Ossenkoppele R, Perrotin A, et al. Clinically diagnosed probable AD cases with a negative amyloid PET scan: clinical findings [abstract IC-P-010]. *Alzheimers Dement*. 2014;10(4)(suppl):12. doi:10.1016/j.jalz.2014.05.014

21. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194.

22. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.

23. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984;141(11):1356-1364.

24. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 1993;43(11):2412-2414.

25. Marcus DS, Olsen TR, Ramaratnam M, Buckner RL. The Extensible Neuroimaging Archive Toolkit: an informatics platform for managing, exploring, and sharing neuroimaging data. *Neuroinformatics*. 2007;5(1):11-34.

26. FDA Advisory Committee briefing document. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM240266.pdf. Accessed July, 2016.

27. Frisoni GB, Jack CR, Winblad B. Alzheimer's disease biomarker development: a call to funding bodies. *Neurobiol Aging*. In press.

28. Ossenkoppele R, Prins ND, Pijnenburg YA, et al. Impact of molecular imaging on the diagnostic process in a memory clinic. *Alzheimers Dement*. 2013;9(4):414-421.

29. Villemagne VL, Ong K, Mulligan RS, et al. Amyloid imaging with (18)F-florbetaben in Alzheimer disease and other dementias. *J Nucl Med*. 2011;52(8):1210-1217.

30. Naasan G, Rabinovici GD, Ghosh P, et al. Amyloid in dementia associated with familial FTLD: not an innocent bystander. *Neurocase*. 2016;22(1):76-83.

31. Monsell SE, Kukull WA, Roher AE, et al. Characterizing apolipoprotein E ε4 carriers and noncarriers with the clinical diagnosis of mild to moderate Alzheimer dementia and minimal β-amyloid peptide plaques. *JAMA Neurol*. 2015;72(10):1124-1131.

32. Serrano-Pozo A, Qian J, Monsell SE, et al. Mild to moderate Alzheimer dementia with insufficient neuropathological changes. *Ann Neurol*. 2014;75(4):597-601.

33. Jack CR Jr, Knopman DS, Chételat G, et al. Suspected non-Alzheimer disease pathophysiology—concept and controversy. *Nat Rev Neurol*. 2016;12(2):117-124.

34. Rowe CC, Ellis KA, Rimajova M, et al. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. *Neurobiol Aging*. 2010;31(8):1275-1283.

35. Mendez MF, Shapira JS, McMurtray A, Licht E. Preliminary findings: behavioral worsening on donepezil in patients with frontotemporal dementia. *Am J Geriatr Psychiatry*. 2007;15(1):84-87.

36. Arciniegas DB, Anderson CA. Donepezil-induced confusional state in a patient with autopsy-proven behavioral-variant frontotemporal dementia. *J Neuropsychiatry Clin Neurosci*. 2013;25(3):E25-E26.

37. Boxer AL, Knopman DS, Kaufer DI, et al. Memantine in patients with frontotemporal lobar degeneration: a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2013;12(2):149-156.

38. Erkinjuntti T, Kurz A, Gauthier S, Bullock R, Lilienfeld S, Damaraju CV. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. *Lancet*. 2002;359(9314):1283-1290.

39. Petersen RC, Thomas RG, Grundman M, et al; Alzheimer's Disease Cooperative Study Group. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med*. 2005;352(23):2379-2388.

40. Bittner T, Zetterberg H, Teunissen CE, et al. Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of β-amyloid (1-42) in human cerebrospinal fluid. *Alzheimers Dement*. 2016;12(5):517-526.

41. Guerra UP, Nobili FM, Padovani A, et al; Recommendations from the Italian Interdisciplinary Working Group. Recommendations from the Italian Interdisciplinary Working Group (AIMN, AIP, SINDEM) for the utilization of amyloid imaging in clinical practice. *Neurol Sci*. 2015;36(6):1075-1081.

42. Boccardi M, Altomare D, Ferrari C, et al; INDIA-FBP Working Group. Do beliefs about the pathogenetic role of amyloid affect the interpretation of amyloid PET in the clinic. *Neurodegener Dis*. 2016;16(1-2):111-117.

43. AMYPAD. Amyloid Imaging to Prevent Alzheimer's Disease. http://www.centroalzheimer.org/sito/ip_amypad_en.php. Accessed July 28, 2016.