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Featured Article

Added value of ¹⁸F-florbetaben amyloid PET in the diagnostic workup of most complex patients with dementia in France: A naturalistic study

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Mathieu Ceccaldi received expertise honoraria from Lilly, GE Healthcare, and Piramal Imaging GmbH. Thérèse Jonveaux has served as PI in clinical trials with Piramal Imaging GmbH, MSD, AXOVANT Lilly, and has been invited as a congress speaker by Novartis. Antoine Verger has nothing to disclose. Pierre Krolak-Salmon has nothing to disclose. Claire Houzard has nothing to disclose. Olivier Godefroy has served at scientific advisory boards (Novartis, Pharnext), received funding for travel speaking honoraria and speaker bureau (Novartis, Lilly, Genzyme, Astrazeneca, Biogen, TEVA, Pfizer, Boeringer, ISPEN, Covidien, BMSquibb), and has received unrestricted research support from Lundbeck, ESAI and Novartis. Trevor Shields has nothing to disclose. Audrey Perrotin is an employee of Piramal Imaging. Rossella Gismondi is an employee of Piramal Imaging. Santiago Bullich is an employee of Piramal Imaging. Aleksandar Jovalekic is an employee of Piramal Imaging. Nicola Raffa is an employee of Piramal

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Abstract

Introduction: Although some studies have previously addressed the clinical impact of amyloid positron emission tomography (PET), none has specifically addressed its selective and hierarchical implementation in relation to cerebrospinal fluid analysis in a naturalistic setting.

Methods: This multicenter study was performed at French tertiary memory clinics in patients presenting with most complex clinical situations (i.e., early-onset, atypical clinical profiles, suspected mixed etiological conditions, unexpected rate of progression), for whom cerebrospinal fluid analysis was indicated but either not feasible or considered as noncontributory ([ClinicalTrials.gov: NCT02681172](https://clinicaltrials.gov/ct2/show/study/NCT02681172)).

Results: Two hundred five patients were enrolled with evaluable florbetaben PET scans; 64.4% of scans were amyloid positive. PET results led to changed diagnosis and improved confidence in 66.8% and 81.5% of patients, respectively, and altered management in 80.0% of cases.

Discussion: High-level improvement of diagnostic certainty and management is provided by selective and hierarchical implementation of florbetaben PET into current standard practices for the most complex dementia cases.

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Keywords:

Alzheimer's disease; Clinical practice; Diagnosis; Patient management; Florbetaben; Amyloid imaging

1. Introduction

Alzheimer's disease (AD) is the most common cause of cognitive impairment, accounting for over 60% of all dementia cases [1]. Dementia experts can diagnose "probable AD" with a sensitivity and specificity of only 71% compared with brain histopathology [2]. As many as 39% of patients diagnosed with non-AD dementia show histopathological features of AD on postmortem examination, while up to 25% of patients with a clinical diagnosis of AD have no amyloid pathology at autopsy [2]. Diagnosis of AD thus remains challenging, especially in younger patients (early-onset dementia), patients with complex clinical presentations (i.e., atypical nonamnestic clinical profiles such as predominant language, visuospatial, or behavioral symptoms), patients with mixed conditions [3], as well as in those presenting with an unexpected rate of progression (see [Supplementary Material](#)) [4,5]. Although disease-modifying medications do not exist yet for AD, timely introduction of an improved diagnostic pathway has the potential to provide actual health benefits to patients presenting with cognitive decline and may also be cost-effective [6]. Uncertainty of diagnosis, especially when it lasts a long time, may have devastating effects on quality of life and health of patients with dementia [7].

AD-specific biomarkers, such as amyloid beta ($A\beta$), are now detectable in vivo and can be measured directly through positron emission tomography (PET) using amyloid-specific ligands [8] or indirectly by assessing $A\beta_{42}$ levels in cerebrospinal fluid (CSF) [9]. Amyloid imaging for detection of neuritic plaques has high sensitivity and specificity compared with histopathology as standard of truth [10–12]. It has been demonstrated that a reduced CSF level of $A\beta_{42}$ in patients with AD is due to $A\beta$ deposition and, thus, reflects plaque (or fibrillar $A\beta$) load in the brain [9]. An inverse relation has been described between CSF $A\beta_{42}$ levels and binding

of amyloid PET tracers in cortical brain regions [13], and the high concordance between CSF $A\beta_{42}$ and amyloid PET imaging (see [Supplementary Material](#) and [9,14]) suggests that they may be used interchangeably to aid clinical diagnosis workup. Although in many countries analysis of CSF AD biomarkers has been accepted as standard practice to improve diagnostic certainty in patients with atypical neurocognitive decline [15], the use of amyloid PET remains restricted to the research setting.

Several past and present studies investigate the cumulative utility of amyloid imaging on the routine clinical diagnostic assessment of large sets of patients evaluated for cognitive impairment in memory clinics (see [Table 1](#)). Population of patients and inclusion criteria of course vary, with respect to the use of appropriate use criteria (AUC) recommendations. Nevertheless, only a few studies have been implemented in natural settings, and specifically in tertiary memory clinics. Finally and above all, none of them selectively used CSF biomarker information to improve diagnostic dilemmas before PET assessment. For example, Zwan et al. [16] included patients with early-onset or mild dementia, who benefited of a lumbar puncture (LP), but CSF results were not disclosed before PET data were available and were not taken into account for the initial diagnosis, thereby altering the natural setting. In daily practice, LP cannot be performed in all patients for whom CSF analysis would otherwise be recommended because of medical reasons such as use of oral anticoagulants or spinal problems or because of patient refusal. Moreover, variability of CSF analyses is common between and within laboratories, in particular for $A\beta_{1-42}$ and phosphorylated tau, which may have a large impact on CSF-based AD diagnosis in clinical settings [32]. Clinicians interpret profiles of CSF biomarkers within a clinical context [33], which, in case of limit values, or partial abnormalities associated with complex clinical

Table 1
Studies on clinical utility of amyloid PET imaging

#ID	Paper	Aβ-PET tracer	Subjects (n)	Study design	Clinical centers	Natural setting	Population (a.restrictive selection, b.uncertainty as selection criterion, c.MCI)	In line with AUC recommendations	Full diagnostic workup	Aβ biomarker sequence (CSF vs. PET)
Literature										
1	Ceccaldi et al., (in prep)	FBB	205	Prospective	18 tertiary memory clinics	Yes	a) Restrictive b) High uncertainty c) MCI excluded	Yes*	Yes	1. CSF 2. Amyloid PET
2	Zwan et al., 2017 [16]	FMM	211	Prospective	Tertiary memory clinic	Yes	a) Restrictive b) Early-onset and mild dementia, uncertainty c) MCI excluded	No	Yes	1. Amyloid PET
3	Weidman et al., 2017 [17]	FBP	16	Case series	NA	No	a) Restrictive b) Cognitive decline and uncertain diagnosis c) MCI included	Yes†	Partially	1. Amyloid PET
4	Apostolova et al., 2016 [18]	FBP	53	Retrospective	NA	No	a) Nonrestrictive b) Early-onset/Late-onset AD c) MCI included	Yes†	No	1. Amyloid PET
5	Boccardi et al., 2016 [19]	FBP	228	Prospective	18 tertiary memory clinics	Yes	a) Restrictive b) Cognitive impairment, uncertainty c) MCI included	No	Yes	1. Amyloid PET
6	Grundman et al., 2016 [20]	FBP	229	Prospective	NA	No	a) Restrictive b) Cognitive decline and uncertain diagnosis c) MCI included	Yes†	Partially	1. Amyloid PET
7	Bensaidane et al., 2016 [21]	NAV	28	Prospective	Tertiary memory clinic	Yes	a) Restrictive b) Atypical AD/unclear c) MCI excluded	Yes†	Yes	1. Amyloid PET
8	Shea et al, 2016 [22]	PIB	102	Retrospective, case series	Memory clinic	Yes	a) Nonrestrictive b) Clinical population c) MCI included	No	Yes	1. Amyloid PET
9	Schönecker et al., 2016 [23]	FBB	33	Case series	Memory clinic	Yes	a) Nonrestrictive b) Uncertain clinical diagnosis c) MCI included	No	Yes	1. Amyloid PET
10	Sanchez-Juan et al., 2014 [24]	PIB	137	Retrospective	NA	No	a) Nonrestrictive b) Cognitive impairment and uncertainty c) MCI included	No	No	1. Amyloid PET
11	Mitsis et al., 2014 [25] (Grundman cohort)	FBP	30	Case series	Tertiary memory clinic	Yes	a) Nonrestrictive b) Cognitive decline c) MCI included	No	No	1. Amyloid PET

(Continued)

Table 1
Studies on clinical utility of amyloid PET imaging (Continued)

#ID	Paper	A β -PET tracer	Subjects (n)	Study design	Clinical centers	Natural setting	Population (a.restrictive selection, b.uncertainty as selection criterion, c.MCI)	In line with AUC recommendations	Full diagnostic workup	A β biomarker sequence (CSF vs. PET)
12	Degerman et al., 2013 [26]	PIB	18	Retrospective	Memory clinic	Yes	a) Nonrestrictive b) Probable AD or FTD c) MCI excluded	No	Yes	1. Amyloid PET
13	Grundman et al., 2013 [4]	FBP	229	Prospective	NA	No	a) Restrictive b) Cognitive decline and uncertain diagnosis c) MCI included	No	Partially	1. Amyloid PET
14	Ossenkoppelle et al., 2013 [27]	PIB	154	Prospective	Tertiary memory clinic	Yes	a) Nonrestrictive b) Clinical population c) MCI included	No	Yes	1. Amyloid PET
15	Frederiksen et al., 2012 [28]	PIB	57	Retrospective	Memory clinic	Yes	a) Nonrestrictive b) Uncertain diagnosis c) MCI included	No	Yes	1. Amyloid PET
16	Schipke et al., 2012 [29]	FBB	121	Retrospective	NA	No	a) NA b) Probable AD and HV c) NA	No	Yes	1. Amyloid PET
Ongoing clinical studies										
17	IDEAS (NCT02420756) [30]	FBB, FMM, FBP	>18,000	Prospective	NA	Yes	a) Restrictive b) Probable AD or MCI c) MCI included	Yes	Yes	1. Amyloid PET
18	ABIDE (EudraCT 2014-000562-21) [31]	FBB	500	Prospective	Tertiary memory clinic	Yes	a) Nonrestrictive b) Mixed c) MCI included	No	Yes	1. Amyloid PET

Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; PET, positron emission tomography; AUC, appropriate use criteria; MCI, mild cognitive impairment; FBB, florbetaben; FMM, flutemetamol; FBP, florbetapir; PIB, Pittsburgh compound C; NAV, Navidea; FTD, frontotemporal dementia; HV, healthy volunteers.

*Haute Autorité de Santé criteria, in line with AUC classification, however inclusion of demented patients only, not including MCI.

[†]Retrospective AUC classification.

[‡]Recommendations of the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia, in line with AUC classification.

situations, may prompt them to consider the CSF results as “noncontributory.” In this clinical context, it is unknown whether amyloid imaging provides cumulative utility in routine clinical diagnostic assessment including collection of CSF. In the present study, we have addressed this issue with a hierarchical approach and applied it to the French clinical setting within a network of tertiary memory clinics and with respect to national recommendations [34].

Florbetaben is a radiopharmaceutical approved in Europe and indicated, in conjunction with clinical evaluation, for PET imaging of A β neuritic plaque density in the brains of adults with cognitive impairment who are being evaluated for AD. A negative scan indicates sparse or no plaques, which is not consistent with a diagnosis of AD.

The present study is the first trial that explores whether florbetaben PET imaging provides added value for the assessment of complex dementia patients without interfering with the current clinical setting, including use of LP wherever possible and in line with current practice in European expert centers [15]. Amyloid PET is only introduced as a “second-line” indication for patients in whom the etiology of symptoms remained uncertain after a complete diagnostic workup and in absence of conclusive CSF results. In detail, the trial investigates whether amyloid PET imaging in patients under investigation for AD for whom LP was either contraindicated or refused, or did not provide conclusive results to the clinician, leads to changes of diagnosis and higher levels of diagnostic confidence and alterations in patient management.

2. Methods

2.1. Participants

Eligible patients were evaluated for AD in tertiary memory centers and had a preliminary uncertain diagnosis after a prior comprehensive workup, according to recommendations from the French Health Authority (HAS) [34]. Because of the diagnostic uncertainty, CSF examination was planned in these patients but was not obtained or not considered helpful by the expert clinician for one of the following reasons: (1) LP was refused by the patient; (2) LP was not feasible for medical reasons; or (3) results of CSF analysis were considered as noncontributory by the clinician (e.g., uninterpretable due to technical problems, values close to threshold, only one abnormal biomarker out of three, only two abnormal biomarkers out of three, or result not consistent with clinical information). All patients, who were included in the study, fulfilled at least one of the AUC as defined by Johnson et al. in 2013 [8] and were in accordance with national recommendations [34]. Full eligibility criteria are provided in the [Supplementary Material](#). All participants or their legal representative provided written informed consent for study participation, visits, and data source verification. The study

was conducted in accordance with the Declaration of Helsinki after approval of Ethics Committees.

2.2. Study design

This was a phase 4 multicenter open-label study ([ClinicalTrials.gov: NCT02681172](https://clinicaltrials.gov/ct2/show/study/NCT02681172)) conducted in the outpatient setting of 18 French tertiary memory clinics, without interfering with the natural clinical setting. All participating clinical sites belong to an established network of university and regional expert centers, which have the mission to contribute to diagnosis of patients with complex clinical situations and provide support for secondary-level structures, that is, private specialists and memory centers in local hospitals. The participating investigators are either neurologists or geriatricians, with a long-standing experience in dementia, sharing homogeneous practices, and with access to a technical platform, including the possibility of performing CSF analyses and functional imaging examinations. Further details of the diagnostic workup in accordance with national guidelines [34] are summarized in [Supplementary Fig. 1](#).

Each patient had three outpatient clinic visits: a screening/baseline visit to record information on previous workups and to establish an initial diagnosis (visit 1), a florbetaben PET scan (visit 2), and a follow-up visit at which patients were informed of the PET scan result and a final diagnosis was established (visit 3). Diagnostic certainty was assessed using a five-point Likert scale. Clinicians could report up to three possible diagnoses for each patient and indicate the probability by rank order. Level 1 was defined as the most probable of up to three potential hypotheses (levels 1–3). Management changes were defined as initiation or withdrawal of any medication, additional diagnostic tests, referral to other specialists, or providing additional explanation or advice for patients and their families. Full details are provided in the [Supplementary Material](#).

2.3. Imaging protocol and visual assessment

Florbetaben PET images were acquired 90–110 minutes after intravenous injection of 300 MBq ($\pm 20\%$) florbetaben according to a standardized acquisition and image-processing protocol [10] established during a technical visit to each center. PET image interpretation was performed locally in each center by nuclear physicians, who had undergone training for appropriate interpretation of scans. For each individual site, florbetaben scans were assessed by the associated nuclear physician. Results were interpreted as either “positive” or “negative” based on regional cortical tracer uptake assessment of the lateral temporal cortex, frontal cortex, posterior cingulate cortex/precuneus, and parietal cortex, as described previously [10].

2.4. Statistical methods

All patients from the full analysis set were included in the per-protocol set, as no major protocol deviations were

reported. To test whether potential added value of florbetaben imaging is present for different patient categories classified according to clinical status, PET categorization, or reason of eligibility, additional subgroups were analyzed (subgroup 1: patients who refused LP; subgroup 2: patients in whom LP was not possible due to medical reasons; subgroup 3: patients with noncontributory results from CSF analysis according to the clinician). These are presented in [Supplementary Tables 2–6](#).

Mean \pm standard deviation values and frequency distributions are reported. Relative frequency and its two-sided 95% confidence interval (Clopper-Pearson) are reported. Change of confidence level is reported by its frequency distribution. Wilcoxon sign rank test is reported for comparison of initial and final confidence levels. Kruskal-Wallis

ANOVA with Dunn's multiple comparisons and Mann-Whitney tests are performed to test variables of different groups. For comparison of frequency data sets, Fisher exact is applied. To test for proportion trends, the Cochran-Armitage test is applied.

3. Results

3.1. Diagnostic workup and diagnosis before PET scan

The full study cohort included 205 patients, of whom 42.4% ($n = 87$) underwent LP ([Fig. 1](#)). Baseline characteristics of patients are shown in [Table 2](#). Based on the prescan diagnostic workup, the most frequent diagnosis hypothesis (probability level 1) was AD (72.2%; $n = 148$); more than

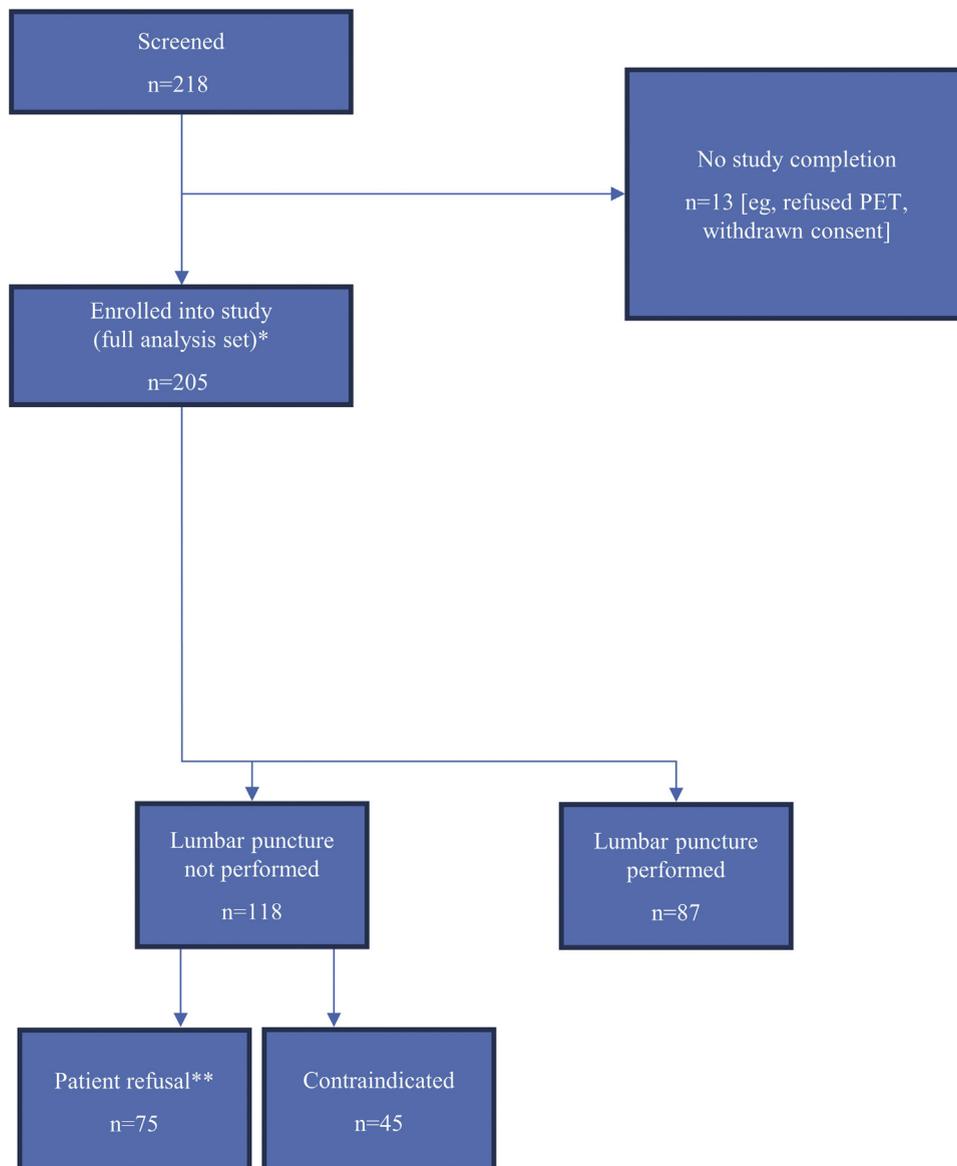


Fig. 1. Patient disposition and subgroups. *All patients who received florbetaben, had a PET/computed tomography image, and in whom etiology of symptoms remained unexplained after a complete diagnostic workup. **Two subjects who refused lumbar puncture were also contraindicated for the procedure. Abbreviation: PET, positron emission tomography.

Table 2
Baseline demographics and clinical characteristics

Full dataset	N = 205	Refused LP*, N = 75	Contraindicated CSF*, N = 45	Noncontributory** CSF, N = 87	P
Age (years), mean \pm SD (median)	70.9 \pm 9.7 (71.0)	74.01 \pm 8.70 (75.19)	72.91 \pm 9.47 (74.07)	66.75 \pm 9.09 (67.39)	<.0001 [§]
Gender, n (%)					
Male	103 (50.2)	35	27	43	
Female	102 (49.8)	40	18	44	
MMSE score***, mean \pm SD (median)	22.1 \pm 5.1 (23.0)	21.96 \pm 4.86 (22)	22.87 \pm 4.72 (24)	21.83 \pm 5.52 (23)	>.05 [‡]
Educational level					
None	2	1	1	0	
Primary school	34	13	10	11	
High school up to 15 years old	53	16	10	27	
High school up to 18 years old	49	20	10	20	
College	67	25	14	29	
Study intervals					
Time between visit 1 and visit 3 in days, mean \pm SD (median)	80.84 \pm 39.30 (72)	85.17 \pm 40.96 (77)	78.24 \pm 34.02 (69)	79.54 \pm 40.31 (74)	>.05 [‡]
Underwent lumbar puncture, n (%) [†]	87 (42.4)				
Ambiguous CSF result	71 (34.6)				
CSF result inconsistent with clinical information	16 (7.8)				
Uninterpretable CSF result for technical reasons	4 (2.0)				
Did not undergo lumbar puncture, n (%)	118 (57.6)				
Patient refusal	75 (36.6)				
Contraindicated or failed	45 (22.0)				
Anticoagulant therapy	16 (7.8)				
Thrombocytopenia	4 (2.0)				
Lumbar puncture failed	8 (3.9)				
Spinal problems	17 (8.3)				

Abbreviations: CSF, cerebrospinal fluid; LP, lumbar puncture; MMSE, Mini-Mental State Examination; SD, standard deviation.

*Two subjects that refused LP were also contraindicated for the procedure.

**Uninterpretable CSF results due to technical problem, ambiguous CSF biomarker results (eg, A β 42, T-tau, P-Tau discordance or values of A β close to the threshold of significance) or divergent results with clinical information.

***Most recent score within the previous 12 months.

[†]Patients may have had more than one reason for noncontributory CSF data.

[‡]Kruskal-Wallis ANOVA with Dunn's multiple comparisons test.

[§]Multiple comparison: Age was significantly lower in the noncontributory subgroup, when compared to the refused and contraindicated categories.

four-fifths of these cases were represented by a complex clinical situation (atypical form, early-onset AD, and rapidly progressive AD) (Table 3). A neurodegenerative (ND) non-AD dementia or mixed dementia was initially suspected in 15.6% ($n = 32$) and 8.3% ($n = 17$) of subjects, respectively. A non-ND cause of dementia was reported in 4.9% ($n = 10$) of subjects. Overall, baseline confidence in the initial diagnosis was moderate (52.3%).

3.2. Scan results

In total, 64.4% of scans (132/205) were evaluated as amyloid positive on florbetaben PET, while 35.6% (73/205) were evaluated as amyloid negative.

3.3. Change in diagnosis, change in diagnostic confidence, and change in management

After PET scan, 66.8% of diagnoses (137/205) were changed (based on all prescan hypotheses). Moreover, the total amount of provided potential hypotheses (levels 1–3)

before and after florbetaben PET disclosure decreased significantly (63.9% [393/615] potential hypotheses at initial diagnosis vs. 43.6% [268/615] potential hypotheses at final diagnosis; $P < .0001$, Fisher exact test). Change of diagnosis was significantly more common for amyloid-negative scans versus amyloid-positive scans (83.6% [61/73] diagnosis changes vs. 57.6% [76/132], respectively; $P < .0001$, Fisher exact test). After PET scan, 62.0% of subjects (127/205) had a dementia diagnosis due to AD. A ND non-AD dementia or mixed dementia was diagnosed in 17.6% (36/205) and 4.9% (10/205) of subjects after scan, respectively. Non-ND causes of dementia were reported in 17.1% of subjects (35/205).

Results were similar for patients grouped according to initial clinical diagnosis (Supplementary Table 2), for patients classified according to PET status (Supplementary Fig. 3), and in the three subsets of patients according to reason of eligibility (Supplementary Table 4). Demographic characteristics and global cognitive level, eligibility criteria, and prior diagnostic workup in the 12 months immediately preceding study entry were compared between patients with changed and unchanged diagnosis and for patients

Table 3
Diagnosis (probability level 1*) before and after scan

Diagnosis (probability level 1),* n (%)	Before scan, N = 205 [†]	After scan, N = 205 [‡]
AD dementia	148 (72.2)	127 (62.0)
Sporadic AD, atypical form	67 (32.7)	43 (21.0)
Early-onset AD	50 (24.4)	40 (19.5)
Sporadic AD, typical form	27 (13.2)	41 (20.0)
Rapid progressive AD (CJD excluded)	4 (2.0)	3 (1.5)
Non-AD dementia (neurodegenerative)	32 (15.6)	36 (17.6)
Frontotemporal lobar dementia	14 (6.8)	17 (8.3)
Primary progressive aphasia	8 (3.9)	6 (2.9)
Lewy body disease	7 (3.4)	8 (3.9)
Corticobasal dementia	2 (1.0)	1 (0.5)
Semantic dementia	1 (0.5)	3 (1.5)
Parkinson's disease	—	1 (0.5)
Mixed dementia	17 (8.3)	10 (4.9)
Nonneurodegenerative dementia	10 (4.9)	35 (17.1)
Psychiatric disorders	3 (1.5)	11 (5.4)
Vascular dementia	2 (1.0)	8 (3.9)
Other	5 (2.4)	16 (7.8)

Abbreviations: AD, Alzheimer's disease; CJD, Creutzfeldt-Jakob disease.

*Clinicians could report up to three possible diagnoses for each patient and indicate the probability by rank order. Level 1 was defined as the most probable of up to three potential hypotheses.

[†]Two patients had two level-1 diagnoses with equal probability.

[‡]Three patients had two level-1 diagnoses with equal probability (most patients had more than one potential hypothesis, illustrating the level of uncertainty and the complexity of the cases).

with and without management changes (Supplementary Tables 5 and 6). The between-group comparison did not show any significant differences on these variables.

Frequencies of the four possible underlying etiologies for diagnosis based on probability level 1 for patients with a changed diagnosis are shown in Fig. 2. Of PET-negative subjects, 95.1% (58/61) fell into a category other than AD after scan result disclosure. Before the scan, only 32.8% (20/61) of these subjects were categorized as other than AD. Similarly, 86.8% (66/76) of PET-positive subjects were diagnosed with AD after PET result disclosure, whereas only 63.2% (48/76) were considered to have some form of AD at initial diagnosis.

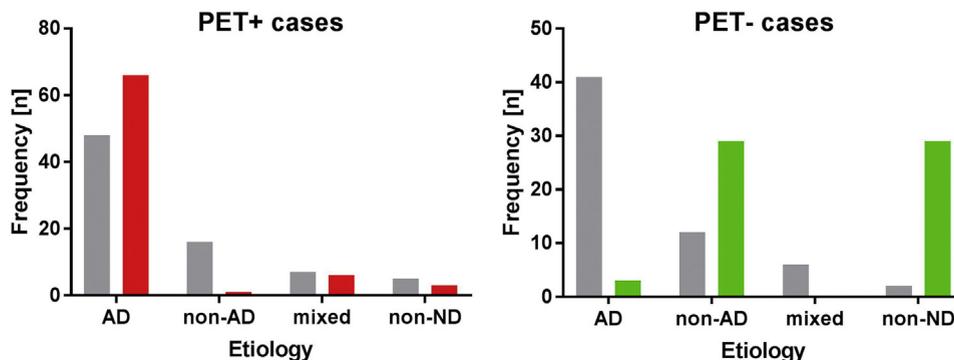


Fig. 2. Etiology of 137 patients with a change in diagnosis after positron emission tomography (PET) scan. Etiology was defined based on level-1 hypothesis of initial diagnosis (gray) and final diagnosis (colored). The data set included 76 subjects with positive PET and 61 subjects with a negative PET; not all changes are based on a level-1 change. Abbreviations: AD, Alzheimer's disease; ND, neurodegenerative; non-AD, neurodegenerative non-Alzheimer's disease; mixed, mixed dementia.

The baseline confidence was moderate (52.3%). Diagnostic confidence improved significantly after PET (Fig. 3), with improved confidence reported for 167/205 cases (81.5%; $P < .0001$), and similar results found across subgroups (Table 4, Supplementary Table 4). Weak and very weak diagnostic confidence was reported in 46 patients (22.4%) at the initial assessment but only in 5 (2.4%) patients after PET result disclosure. Confidence was significantly improved for amyloid-positive scans compared to amyloid-negative scans (116/132 [87.9%] vs. 51/73 [69.9%], $P = .002$, Fisher exact test, Table 4). Most of the changes included an improvement by one category ($n = 94$ subjects, Fig. 3), and overall diagnostic confidence improved by 30.2% leading to a confidence of 82.6% after PET disclosure.

Changes in management were reported for 80.0% (164/205) of patients (Table 5); they were independent of amyloid status (amyloid positive 106/132 [80.3%], amyloid negative 58/73 [79.5%]; $P > .05$, Fisher exact test). Initiation of new medication was mainly reported after disclosure of amyloid-positive PET scans, whereas withdrawal of medication was exclusively reported for amyloid-negative PET scans (Supplementary Fig. 4). Substantial management changes (i.e., any change in initiation or withdrawal of medication, additional diagnostic tests, or referral to a new specialist) were reported in 50.7% (104/205) of patients (Table 5). Results were similar for different subgroups (Supplementary Table 4). Two exemplary clinical cases are presented in Supplementary Fig. 2.

Increase in confidence, change in diagnosis, and change in management after PET were correlated with the initial diagnostic confidence. All three parameters were changed more often or showed a stronger increase for subjects with lower pre-PET diagnostic certainty (Supplementary Fig. 3).

4. Discussion

This is the first clinical prospective study that has sought to define the impact of amyloid PET on diagnosis and management in cases corresponding to the highest level of diagnosis uncertainty—early-onset dementia and atypical

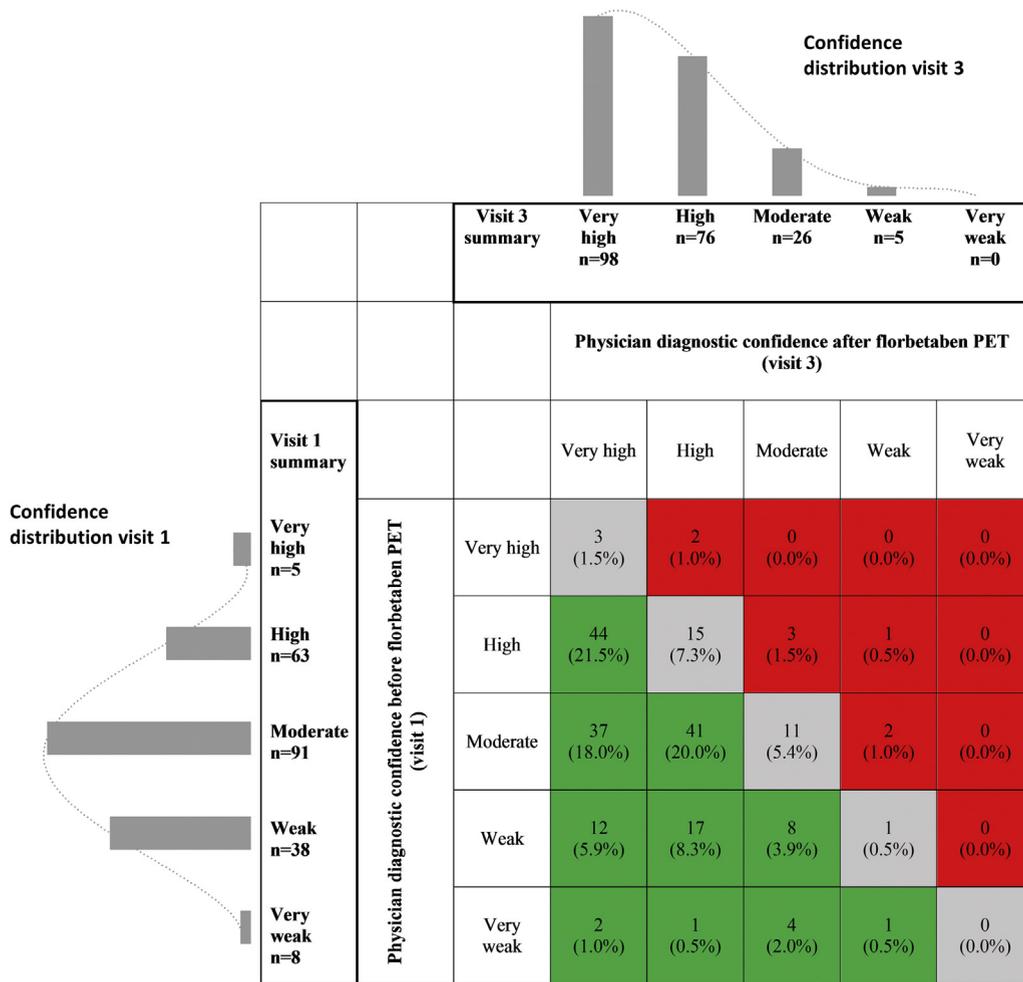


Fig. 3. Diagnostic confidence before and after florbetaben positron emission tomography (PET) and change in diagnostic confidence (per-protocol population).

nonamnesic clinical profiles (e.g., predominant language, visuospatial, or behavioral symptoms, and unexpected rate of progression) [34,35]—without interfering with the specific processes applied in the naturalistic setting of tertiary memory clinics. Because of a long-established national implementation of LP in the workup for such complex clinical situations, a hierarchical diagnostic design was adopted, with amyloid PET imaging being positioned “second line” and only considering patients that did not benefit from a recommended AD biomarker assessment using CSF.

In detail, the present study population consisted of patients eligible for CSF evaluation but in whom LP was refused by the patient or was not feasible due to medical reasons, or in whom CSF results were judged by clinicians to be noncontributory (i.e., ambiguous or inconsistent with the clinical profile). In these patients, visual interpretation of florbetaben PET led to a high percentage of clinicians (66.8%) altering their initial diagnosis. Previous studies investigating the influence of amyloid imaging on diagnostic evaluation in a more general context report change rates of diagnosis between 9.5% and 54.6% [4,16,19,24,27,29,36]. The high proportion of diagnostic changes reported here is

most likely a result of the high-level diagnostic uncertainty in this very complex population. This hypothesis is supported by the finding that changes in diagnosis were statistically more common in patients with lower pre-PET diagnostic certainty within this study cohort.

Although it is demonstrated in previous studies that Aβ42 measurements in the CSF and amyloid PET are correlated and are often interchangeable for the purpose of diagnosing AD, it is not clear how different biomarkers (both CSF and PET) relate in patients with such complex presentations. For example, a recent study showed that CSF profiles in atypical AD are more heterogeneous than what is reported in typical AD subjects [37]. In the light of the already complex clinical situations of the included patients and from the clinician’s point of view, ambiguous CSF profiles did not provide further insights to solve those clinical dilemmas and diagnoses were still formulated with relatively low certainty. This is in line with previous findings, showing that clinicians are influenced by CSF AD biomarkers; however, diagnosis changes are not reported for ambiguous CSF biomarker constellations [38]. The concrete impact of ambiguous CSF results on diagnosis and patient

Table 4
Change in diagnosis and diagnostic confidence

Amyloid status on florbetaben PET	
Independent of amyloid status	<i>N</i> = 205
Change in diagnosis, <i>n</i> (%) [95% CI]	137 (66.8) [59.9–73.2]
Improved confidence, <i>n</i> (%) [95% CI]	167 (81.5) [75.5–86.5]
Amyloid positive	<i>N</i> = 132
Change in diagnosis, <i>n</i> (%) [95% CI]	76 (57.6) [48.7–66.1]
Improved confidence, <i>n</i> (%) [95% CI]	116 (87.9) [81.1–92.9]
Amyloid negative	<i>N</i> = 73
Change in diagnosis, <i>n</i> (%) [95% CI]	61 (83.6) [73.0–91.2]
Improved confidence, <i>n</i> (%) [95% CI]	51 (69.9) [58.0–80.1]

Abbreviations: CI, confidence interval; PET, positron emission tomography.

management changes was not evaluated in this study, and thus, the diagnostic impact of CSF cannot be derived. Further analysis on the relationship between CSF markers, amyloid imaging, and clinical findings in such a population is important to understand the details of such complex patients.

As reported in earlier studies [16,27], change in diagnosis was correlated with confidence in the initial diagnosis. Change in diagnosis was particularly frequent when PET scan was negative (83.6% of cases), which is also in line with previous findings [19]. Given the high negative predictive value of amyloid imaging in histopathology studies [10], this result is not surprising and indicates that a negative amyloid scan is generally used by dementia experts as a validated method to exclude a diagnosis of AD in most complex cases. Of the 61 PET-negative subjects with a changed diagnosis, only 3 (4.9%) were considered to be AD after florbetaben assessment, while 41 (67.2%) were

Table 5
Change of management plan

Amyloid status on florbetaben PET	
Independent of amyloid status	<i>N</i> = 205
Change, <i>n</i> (%) [95% CI]	164 (80.0) [73.9–85.2]
No change, <i>n</i> (%)	41 (20.0)
Changes of management, <i>n</i> (%)	
New medication initiated	71 (34.6)
Medication withdrawn	8 (3.9)
Additional diagnostic tests	17 (8.3)
Referred to another specialist	16 (7.8)
Offered additional explanation [†]	105 (51.2)
Offered additional advice [‡]	60 (29.3)
Other	57 (27.8)
Strong change of management plan as listed*, <i>n</i> (%)	104 (50.7)
Amyloid positive	<i>N</i> = 132
Change, <i>n</i> (%) [95% CI]	106 (80.3) [72.5–86.7]
Amyloid negative	<i>N</i> = 73
Change, <i>n</i> (%) [95% CI]	58 (79.5) [68.4–88.0]

Abbreviations: CI, confidence interval; PET, positron emission tomography.

*Defined as initiation or withdrawal of medication, additional diagnostic tests, or referral to another specialist.

[†]Offered additional explanation of diagnosis/testing results.

[‡]Patient and/or family offered additional advice on potential daily living/safety concerns.

categorized as AD before scan. Similarly to what has been previously acknowledged for CSF [39], our findings suggest that clinicians do not view amyloid PET in a vacuum but instead consider its utility in combination with other clinical details and available assessments to establish decisions.

Diagnostic confidence increased for 81.5% of the subjects after PET result disclosure, and the strongest confidence increases were observed in subjects with relatively low certainty in the initial diagnosis. Most of the changes included a confidence increase by one category leading to an overall diagnostic increase of 30.2% after disclosure of PET results, which is higher than most previously reported values [4,19,21]. However, given the very low diagnostic confidence at baseline, the particularly distinct impact is not surprising and in general in alignment with previous studies. For example, change in diagnosis and increase in diagnostic confidence were lower in studies with higher pre-PET diagnostic confidence [4,27]. It is thus hypothesized that amyloid PET scans have the greatest impact in situations with significant diagnostic concerns after a standard workup has been completed before PET. This is supported in at least one trial [21]. In the present study, the general confidence increase was also reflected by a reduced number of provided diagnosis hypotheses after PET disclosure.

After florbetaben PET, changes in management were reported for 80.0% of patients. Even when considering only management changes presumed to have a substantial impact on patients (i.e., new medication initiated, medication withdrawn, additional diagnostic tests, referred to another specialist), changes were still reported for 50.7% of patients. These results are in line with an earlier study that used similar criteria, with changes in management reported in 87% of patients after amyloid PET [4]. In other studies of amyloid PET, however, fewer management changes were reported (range, 37%–68%) [16,40]. Various factors, such as differences in methodological definitions, selected variables of patient management, and diagnostic uncertainty before PET assessment, may have contributed to the differences in findings. Interestingly, changes in management were more common in patients with low pre-PET diagnostic confidence.

One concern of the study design is that patients who present medical contraindications that prevent LP, patients who refuse LP, and patients in whom an LP has been achieved might represent significantly different populations. We analyzed these subgroups and found no differences in the distribution of level-1 pretest diagnosis; the percent positive or negative scans; or percent change in diagnosis, diagnostic confidence, or management.

Although the diagnostic accuracy of amyloid PET tracers has been thoroughly assessed in several pivotal histopathology studies [10–12], such information cannot be available in the context of clinical utility studies. Clinical follow-up of the population may provide additional and long-term insights on the impact of amyloid PET on diagnostic and patient management changes.

Another limitation of the present study was the binary visual readout of amyloid PET scans. Although this approach reflects clinical routine usage, we cannot make further statements related to potentially ambiguous PET cases. Previous publications have demonstrated high concordance between visual assessment and quantification methods [41–43], and therefore, semiquantitative approaches may provide adjunct information that might be useful, particularly, for ambiguous cases close to standardized cutoffs. Finally, factors such as degree of experience with amyloid and the physician's beliefs on the clinical value of amyloid imaging may influence interpretation of results and were not controlled for in the study.

The present study was designed with reference to a specific health care model and was restricted to an established network of tertiary memory centers. It focused on a highly selected patient population and included a hierarchical positioning of AD biomarkers, with CSF collection in first line. Several other utility studies are currently being conducted and will further contribute to our knowledge on the impact of amyloid imaging in larger clinical scenarios such as the Imaging Dementia—Evidence for Amyloid Scanning initiative which will enroll >18,000 patients, following AUC recommendations put forward by Johnson et al. [8].

In conclusion, this naturalistic study provides evidence that visual interpretation of florbetaben PET has a strong impact on diagnostic outcome parameters and management of patients in whom uncertainty is particularly common—that is, in early-onset, atypical, mixed, and rapidly progressing presentations—even when they firstly benefited from expert centers' assessments. Given the general diagnostic validity of amyloid PET and the previously reported high concordance rates between imaging and CSF A β 42 levels [9,13,36], it is obvious that PET can efficiently substitute LP in absence of valuable CSF results. Moreover, this study shows that outcome measures of initial assessment are significantly improved in most complex cases. Most patients from this study share a very low pre-PET confidence in the initial diagnosis. There is an ethical imperative to establish an early, validated diagnosis wherever possible [44]. Moreover, it has been shown that a clear diagnosis has a positive impact on caregivers of dementia patients [21]. Providing a higher quality of diagnosis, in terms of unambiguity, may directly contribute to increase the positive impact of memory assessment services on patients' health-related quality of life [45]. From this point of view, our results highlight the immediate clinical utility of amyloid PET imaging for patients with complex dementia presentations in the context of the existing health care framework.

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Authors' contributions: The study was initiated by the principal investigators (Mathieu Ceccaldi and Eric Guedj) together with the sponsor, who supported the collection, analysis, and interpretation of the data, and the writing of the article. The principal investigators had full access to the study data and had final responsibility for the decision to submit for publication. Mathieu Ceccaldi, Rossella Gismondi, Nicola Raffa, Andrew Stephens, and Eric Guedj participated in the initiation, design, and concept of the study; performed data acquisition; were involved in data analysis; and drafted the article. Thérèse Jonveaux, Antoine Verger, Pierre Krolak-Salmon, Claire Houzard, Olivier Godfroy, Trevor Shields, Audrey Perrotin, Florence Pasquier, Franck Semah, Bruno Dubois, Marie-Odile Habert, David Wallon, and Mathieu Chastan performed data acquisition and were involved in article preparation and review. Santiago Bullich participated in the design of the study, was involved in data analysis, and drafted the article. Aleksandar Jovalekic was involved in data analysis and drafted the article.

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Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jalz.2017.09.009>.

RESEARCH IN CONTEXT

1. Systematic review: Although several studies investigated the clinical impact of amyloid positron emission tomography (PET) imaging, none has specifically addressed its selective and hierarchical implementation in relation to cerebrospinal fluid analysis in a naturalistic setting.
2. Interpretation: Whether amyloid PET provides cumulative utility in routine diagnostic assessment in complex patients with an unresolved cerebrospinal fluid biomarker status is unknown. We have addressed this issue with a hierarchical approach within a network of tertiary memory clinics in France and provide robust evidence on the value of amyloid PET.
3. Future direction: Our results highlight the immediate clinical utility of amyloid PET imaging for patients with complex dementia presentations and high levels of diagnostic uncertainty in the context of the existing health care framework. Additional health outcomes and economic data are required to assess the cost-effectiveness of amyloid PET in clinical routine.

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