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Research Report

Initial Physician Experience with [^{18}F]Flutemetamol Amyloid PET Imaging Following Availability for Routine Clinical Use in Japan

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Abstract.
Background: Brain amyloid is a neuropathological hallmark of Alzheimer's disease (AD). By visualizing brain amyloid, positron emission tomography (PET) may influence the diagnostic assessment and management of patients with cognitive impairment.
Objective: As part of a Japanese post-approval study to measure the safety of [^{18}F]flutemetamol PET, the association of amyloid PET results with changes in diagnosis and diagnostic confidence was assessed.
Methods: Fifty-seven subjects were imaged for amyloid PET using [^{18}F]flutemetamol at a single Japanese memory clinic. The cognitive diagnosis and referring physician's confidence in the diagnosis were recorded before and after availability of PET results. Imaging started approximately 90 minutes after [^{18}F]flutemetamol administration with approximately 185 MBq injected. PET images were acquired for 30 minutes.
Results: Amyloid PET imaging led to change in diagnosis in 15/44 clinical subjects (34%). Mean diagnostic confidence increased by approximately 20%, from 73% pre-scan to 93% post-scan, and this rise was fairly consistent across the main patient subgroups (mild cognitive impairment, AD, and non-AD) irrespective of the pre-scan diagnosis and scan result.
Conclusion: The study examined the utility of amyloid PET imaging in a Japanese clinical cohort and highlighted the use of an etiological diagnosis in the presence of the amyloid scan. [^{18}F]Flutemetamol PET led to a change in diagnosis in over 30% of cases and to an increase in diagnostic confidence by approximately 20% consistent with other reports.

Keywords: Alzheimer's disease, amyloid imaging, dementia, diagnosis, [^{18}F]flutemetamol, mild cognitive impairment, PET, safety

INTRODUCTION

As the world's population ages, the global burden of dementia and related neurodegenerative conditions increases rapidly. Over 45 million people worldwide were suffering from dementia in 2015, and the

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number is projected to almost double every 20 years [1]. In Japan the dementia burden is more than 4.6 million people [2]. Alzheimer's disease (AD) is the predominant dementia type in Japan, accounting for approximately 65% of all cases [3].

The pathophysiological changes underlying AD (deposition of amyloid and tau) begin long before cognitive symptoms appear [4]. Early diagnosis of AD is therefore important to support planning of care for affected individuals, as well as access to standard or investigational treatment options [5]. However, accurate diagnosis of AD is challenging, especially in the early stages of the disease. Standard clinical assessments have limited ability to reliably distinguish AD from non-AD related dementias [6]. For example, the NINCDS-ADRDA clinical criteria for AD assessment were found to have good sensitivity (ranging from 71–87%), but lower specificity (in the range of 44–71%), using autopsy as the standard of truth [6]. Biomarkers have considerable potential to improve the diagnosis and exclusion of AD, and recent research diagnostic guidelines for AD and its prodromal stages call for the inclusion of one or more pathophysiological biomarkers to support clinical assessment [7–9].

Brain amyloid accumulation is considered a relevant early biomarker for AD pathology [10], and can be detected by *in vivo* positron emission tomography (PET) imaging using radiolabeled tracers with a high affinity for amyloid-β [11, 12]. In addition to the ^{11}C Pittsburgh compound B ([^{11}C]PiB), extensively studied as an amyloid PET tracer in research settings, fluorine-labeled tracers ([^{18}F]florbetapir [13, 14], [^{18}F]florbetaben [15, 16], and [^{18}F]flutemetamol [17, 18]) have been developed and approved for clinical use in the USA, Europe, and Japan to detect or exclude the presence of amyloid-β plaques in the brains of living patients.

In a previous Phase II study in Japanese subjects, [^{18}F]flutemetamol PET safely differentiated subjects with probable AD from healthy volunteers [19]. These data helped support the approval in Japan of [^{18}F]flutemetamol for visualizing neuritic amyloid deposition [20]. The cases reported here are a cohort of clinical cases from a single center who participated in a prospective, observational, post-approval surveillance study to further assess the safety of [^{18}F]flutemetamol PET in routine use.

Of scientific interest to the neurology community was the assessment of the impact of [^{18}F]flutemetamol images on clinical diagnoses and the referring physician's confidence in the pre- and post-imaging diagnosis, the results of which form the main part of this research paper.

METHODS

Ethics

Study conduct was in accordance with Good Post-Marketing Study Practice, as governed by applicable regulations in Japan. As this was an observational post-marketing surveillance study, no Ethics Committee or Independent Review Board consultation was required for the clinical cases examined, in accordance with applicable national and local laws and regulations. Since the site had no previous experience in the use of the PET tracer, a number of cognitively normal subjects were also included in order for the local physicians to gain familiarity in tracer handling, scanning procedures, and the appearance of negative [^{18}F]flutemetamol images acquired with their own PET cameras. Imaging of these cognitively unimpaired subjects was subject to local consenting arrangements.

Recruitment of cases

At a single Japanese memory clinic subjects scheduled for a [^{18}F]flutemetamol scan as part of clinical practice in Japan were screened for eligibility and willingness to participate. Referring physicians were not bound to follow the amyloid PET Appropriate Use Criteria [21] and subjects were included by the local physician if he considered that the result of the amyloid scan would add value to his diagnostic work-up/clinical assessment. This study is descriptive in nature and the site enrolled 57 subjects. Under local regulations, informed consent was not required from patients as they received [^{18}F]flutemetamol as part of clinical practice. A number of cognitively unimpaired/normal subjects were also included as per above (see ethics section).

For data analysis, the subjects were grouped into 6 clinical categories based upon syndromic definitions with subgroups for each category based on the proposed etiological diagnosis: 1) cognitively unimpaired, 2) subject cognitive decliners (SCD/'worried well') (according to the criteria of Jessen et al.) [22], 3) mild cognitive impairment (MCI, sub-grouped by possible etiology), 4) Alzheimer's dementia (sub-grouped as possible or probable AD), 5) other dementia (sub-grouped by dementia of unknown origin, dementia with Lewy

bodies (DLB), frontotemporal dementia (FTD) and other) and 6) non-dementia subjects.

Safety assessments

Baseline characteristics and medical history were recorded for all subjects. Subjects were closely observed for adverse effects from the start of [^{18}F]flutemetamol administration until discharge from the imaging center.

Procedure for clinical work up and [^{18}F]Flutemetamol PET imaging and interpretation

The clinical diagnosis related to the referral for [^{18}F]flutemetamol PET scanning (pre-scan diagnosis) and the referring physician's level of confidence (0% confidence was considered 'not at all confident' and 100% was considered 'completely confident') in the diagnosis were recorded before the administration of the PET tracer. Although subjective, the 0%–100% confidence scale has been used on multiple occasions and has been summarized in a recent review [23]. Patients and a number of cognitively normal individuals received [^{18}F]flutemetamol manufactured onsite using the approved commercially available radiopharmaceutical synthesizing equipment FASTlab (GEMS PET Systems AB, Sweden) [20].

The approximate administered activity of [^{18}F]flutemetamol (manufactured onsite using GE Healthcare FASTlab) was 185 MBq. PET imaging started approximately 90 min after [^{18}F]flutemetamol administration. PET images were acquired for 30 min in all subjects. Cameras used for the acquisition of the images were either a Discovery MI PET/CT (GE Healthcare) or Eminence-G (Shimadzu). Images were reconstructed using iterative reconstruction techniques.

The reader at the site was trained in the interpretation of [^{18}F]flutemetamol PET scans using the approved image training instructions provided by the manufacturer [24, 25] and assessed all images as positive or negative for moderate to frequent neuritic amyloid plaques. Confidence in the [^{18}F]flutemetamol PET scan classification on a 0–100% scale where 0% was no confidence and 100% was very high confidence in the image interpretation was also recorded.

The [^{18}F]flutemetamol image interpretation was then disclosed to the referring physician, and a post-scan diagnosis and confidence score (again using the 0%–100% scale) were recorded within four weeks of receiving the PET scan results.

The impact of [^{18}F]flutemetamol PET images on diagnosis and on the referring physician's level of diagnostic confidence pre- and post-scan was evaluated was evaluated as changes in percentages (i.e., with simple descriptive statistics used) as well as recording the numbers of subjects for whom the diagnosis was either confirmed or changed as a result of the scan.

RESULTS

Demographics

Between July 2016 and December 2017, the site (Table 1) enrolled a total of 57 subjects aged 31 to 96 (30 males and 27 females), including 13 cognitively normal subjects aged 44–73. The remaining 44 subjects were patients being evaluated in clinical practice. The most common medications taken concomitantly or prior to PET imaging were donepezil hydrochloride and memantine hydrochloride.

According to the pre-scan diagnosis, there were 13 normal subjects, 2 worried well, 13 cases of MCI, 11 cases of Alzheimer's dementia, 14 cases of other dementia (dementia of unknown origin., DLB, FTD and other) and 4 cases of non-dementia (mood/epilepsy/depression and sleep disorder). See Table 1 for demographics.

Adverse events

One adverse event was reported in 1 subject (1.8%): a mild, non-serious hot flush, which started immediately after administration of [^{18}F]flutemetamol and resolved within 5 min without intervention. There were no adverse event-related discontinuations or withdrawals after administration of PET tracer and no deaths were reported.

Image interpretation data

Scan results

[^{18}F]Flutemetamol scans were interpreted visually according to imaging reading instructions provided by the manufacturer (GE Healthcare) which also included a test to demonstrate competence to read.

56/57 scan results were available and considered interpretable. See Table 1 for the scan results. One scan was unavailable due to technical issues. 37/56

Table 1
Demographic Data and Scan Results

Subject Grouping	Clinical Group	Number subjects	Age range	M/F ratio	Negative/Positive Scans
1	Cognitively Normal	13	44–73	9/4	13/0
2	SCD ('worried well')	2	51–67	2/0	1/1
3	MCI	13	51–84	7/6	11/2
3a	*MCI due to AD*	*6*	*51–80*	*4/2*	
3b	*MCI due to non-AD*	*4*	*67–84*	*2/2*	
3c	*MCI due to LBD*	*3*	*68–83*	*1/2*	
4	Alzheimer's Dementia	11	59–90	5/6	2/9
4a	*Possible AD*	*3*	*59–82*	*0/3*	
4b	*Probable AD*	*8*	*67–90*	*5/3*	
5	Other Dementia *	14	66–96	6/8	6/7 (+1 scan n/a)
5a	*Unknown Dementia*	*4*	*83–96*	*2/2*	
5b	*DLB*	*7*	*69–86*	*3/4*	
5c	*FTD*	*2*	*66–73*	*1/1*	
5d	*other*	*1*	*84*	*0/1*	
6	Non-dementia**	4	31–76	1/3	4/0

*Dementia of unknown origin (3), Dementia + AD (1), DLB (4), DLB + AD (2), DLB or iNPH (1). **unspecified mood/epilepsy/depression/rapid eye movement sleep behavior disorder. AD, Alzheimer disease; MCI, mild cognitive impairment; LBD, Lewy body dementia; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia.

were classified as negative and 19 considered positive. All the 13 cognitively unimpaired subjects had a negative scan and within the clinical cases, the percentage distribution between negative/positive was 56%/44% (24/19 respectively) (Table 1). Reader confidence in image interpretation was high with a median confidence of 100% (37 of 57 [65%] cases had 100% confidence in the read). 19/57 (33%) had a confidence of 70–98% and there was a single image where the confidence was low at 20% with an unexplained decrease in the uptake of radioactive PET signal in the whole brain.

In the MCI group, the majority of scans were negative (11/13), while in the AD group the majority were positive (9/11). In the 'other dementia' group, the ratio was 7/6 positive to negative with one scan result being unavailable due to technical issues. In the non-dementia group (mood/epilepsy/depression and sleep disorder in the primary diagnosis), all 4 scans were negative. (Table 1).

Overview of diagnostic changes

Among the 44 patients, 15 had a change in diagnosis as a result of the scan. The split of diagnostic changes amongst the subgroups was as follows: 1 (50%) of 2 SCD/worried well, 6 (46%) of 13 MCI, 2(18%) of 11 AD, 6 (43%) of 14 other dementia, and 0 (zero) of 4 non dementia subjects. A summary of the cases where diagnostic changes were observed is shown in Table 2.

Among the MCI cases, most changes were observed in cases where there was a negative scan and hence the prior diagnosis of MCI due to AD was revised to MCI due to non-AD. In other cases, a negative scan led the physician to change the diagnosis from MCI due to AD to either depression or a mood disorder. A positive amyloid scan in an MCI due to non-AD led to a revised diagnosis of MCI due to AD.

Where Alzheimer's dementia was included as the primary diagnosis the proportions of scans with revised diagnostic change were low, with only 2/11 scans being negative. In this group, the patients were classified as either possible AD or probable AD according to the classification of McKhann et al. [9]. The initial designation of AD cases as possible or probable was reflected in the confidence in the pretest confidence in diagnosis (50–60% for possible, 80–100% for probable AD) with the confidence rising after a positive amyloid scan. The two negative scans led to a revision from possible AD to dementia of unknown origin and MCI due to non-AD.

In the cases where other dementias were suspected, a positive scan led to an etiological diagnosis of AD being included in the overall diagnosis (for example AD and DLB, probable AD). In the one negative case where unknown dementia (with possible AD) was initially considered, the diagnosis was revised to DLB.

Changes in diagnostic confidence after amyloid PET scanning

Diagnostic confidence pre- and post-amyloid [^{18}F]flutemetamol PET scan was captured for the

Table 2
Summary of Diagnostic Changes

Subject Grouping	Pre-scan Diagnosis	Scan Result	Post-Scan Diagnosis	No of cases
2	SCD ('worried well')			
	Screening of 'worried well'	Positive	Future Risk for AD (preclinical AD)	1
3	MCI			
	MCI due to AD	Negative	Mood disorder	1
	MCI due to AD	Negative	MCI due to non-AD	3
	MCI due to AD	Negative	Depression	1
	MCI due to non-AD	Positive	MCI due to AD	1
4	Alzheimer's Dementia			
	probable AD	Negative	MCI due to non-AD	1
	possible AD	Negative	Dementia of unknown etiology	1
5	Other Dementia			
	Unknown Dementia	Positive	Suspected AD	1
	Unknown Dementia with AD	Negative	Dementia due to DG and LBD	1
	DLB	Positive	AD and DLB	1
	DLB	Positive	DLB with AD	1
	DLB or iNPH	Positive	AD with DLB or iNPH	1
	FTLD	Positive	Probable AD	1
				total = 15/44

AD, Alzheimer disease; MCI, mild cognitive impairment; DG, degeneration; LBD, Lewy body disease; DLB, dementia with Lewy bodies; iNPH, idiopathic normal-pressure hydrocephalus; FTLD, frontotemporal lobe dementia.

Table 3
Change in Diagnostic Confidence Pre and Post PET Scanning

Group	Clinical Group	Pre-test % confidence in Dx (& range)	Post-test % confidence in Dx (& range)	Average % Change
2	SCD ($n = 2$)	85% (85, 85)	90% (80,100)	5%
3	MCI ($n = 13$)	74% (60–90)	98% (90–100)	24%
4	Alzheimer's Dementia ($n = 11$)	78% (50–100)	96% (80–100)	18%
5	Other Dementia ($n = 14$)	70% (50–90)	94% (60–100)	24%
6	Non-dementia ($n = 4$)	54% (20–80)	80% (30–100)	26%
	Overall	73%	93%	20%

purposes of understanding how the scan influenced physician confidence. Overall in the patient cases ($n = 44$), the pretest confidence was approximately 73% and rose to 93% after the scan result was available indicating that in general the scan added a 20% rise in confidence (Table 3).

Possible AD cases had a much lower percentage confidence in diagnosis (range 50–60%) than probable AD (range 80–100%) and with a positive amyloid scan confidence reached 100% in most of all cases. In the MCI group, the pre-test percentages in confidence were approximately 74% with the scan results driving confidence up to 90–100% irrespective of whether the scan result was positive or negative. In the 'other dementia' groups the percentage pre-test confidence was variable with a range from 50 to 90%. Again, after the scan the mean confidence in this group showed an approximate rise of 24% from 70 to 94% in this group. There were no obvious patterns in either the amyloid positive or negative groups or whether the diagnosis was changed or remained hence these mean changes were not presented and only the overall changes in diagnostic confidence were shown in Table 3.

Overall these results indicate that a scan result inconsistent with the pre-scan clinical diagnosis can result in reconsideration of the diagnosis, and that a scan result that is consistent with the pre-scan diagnosis can result in increased confidence in the original diagnosis. The results also highlight the use of etiological terminology when describing the clinical disease in combination with a pathological component.

Description of near-term management changes

Although collection of management changes was not formally collected in the case records for this analysis, we discussed with the referring physicians how the results of the PET scan influenced patient management. Scan results and images were frequently used in prognostic discussions with patients. For example, if the scan was amyloid-positive, the possibility of disease progression and possible cognitive decline

was discussed with the patient and their family. On the other hand, when a scan was negative, the exclusion of the AD diagnosis was indicated, along with the possible need for further diagnostic testing to identify the patient's cognitive disorder. Medications might be left unchanged if the scan result was expected, but if the scan result was unexpected then additional medications such as memantine or rivastigmine might be added to suppress behavioral symptoms.

DISCUSSION

The first clinical experience in Japan with [^{18}F]flutemetamol following its approval is reported. [^{18}F]Flutemetamol was safe when used in clinical practice within the cases collected at the site. Only one subject (a male aged 47, cognitively unimpaired subject) experienced an adverse event, a mild, non-serious hot flush that resolved spontaneously within 5 min.

The cases included in this paper provided an opportunity to examine the impact of amyloid status information on physicians' working diagnosis and diagnostic confidence in a real-world cohort of subjects scheduled for amyloid PET imaging in Japan.

Interestingly, in this real world setting the cases included were not restricted to those in the appropriate use criteria (AUC) (i.e., atypical AD, unexplained MCI, and early onset AD). Similar experience has been noted by other investigators; for example, in the unselected memory clinic cohort of de Wilde et al. [26], only half of the population of over 500 cases were consistent with the AUC.

The use of amyloid PET led to a revised diagnosis in 15 of 44 clinical cases (34%). For analysis of diagnostic change, cases were split into subgroups relating to initial cognitive function (SCD ('worried well'); MCI, Alzheimer's dementia, other dementias, and non-dementias. In the three major subgroups (MCI, AD, and non-AD), diagnostic change was recorded. The primary change in the MCI group was when the pre-test diagnosis was deemed to be MCI due to AD with a negative scan yielding a subsequent reworking of the diagnosis to MCI due to non-AD. Negative scans also led the physician to consider other clinical presentations (mood disorder and depression). In the Alzheimer's dementia subgroup, the diagnosis was unchanged in 12/14 cases; those with a negative scan were changed to either MCI due to non-AD or dementia of unknown etiology. Those in other dementia categories had an AD component added to their diagnosis with a positive scan (i.e., a mixed dementia, e.g., AD with DLB or with normal-pressure hydrocephalus).

One interesting case was a 'worried well' subject (male aged 51) who also had a positive scan and was reclassified as pre-clinical AD. The rate of amyloid positivity in subjects with subjective cognitive decline with self-reported 'worries' has been reported to be 23% [27] and therefore it could have been expected that a positive scan in one of these cases might have been observed. As stated in Jessen et al. [22], SCD presentation in the worried well group can be a cognitive presentation of prodromal AD. Unlike other biomarkers, amyloid PET can directly visualize amyloid burden in the living human at a very early stage of pathological deposition [10].

All included cases point to the use of the etiological terminology in helping to classify the clinical syndrome (IWG-2 [28, 29]). Indeed, it is recognized that AD-related pathology is seen as a continuum and the disease is now commonly defined as a clinical-biological entity [30].

Considerable evidence supports the use of amyloid PET for accurately detecting brain amyloid in patients along the AD continuum [12, 31–33]. Beyond validation of PET amyloid as a research biomarker, questions of its utility in clinical practice are also being addressed [34–39]. Studies on the impact of amyloid PET in aiding differential diagnosis, improving diagnostic confidence, or influencing patient management have been analyzed at individual patient or summary level [23, 40].

In patients with early-onset dementia and an uncertain clinical diagnosis, [^{18}F]flutemetamol PET altered diagnosis in 19% of 211 patients and increased overall diagnostic confidence from 68% to 88% (in over 85% of patients) [39]. Most patients in this cohort (76%) had a pre-PET diagnosis of AD. In 37% of the patients, amyloid PET led to changes in the management plan, most commonly the initiation of AD medication in amyloid-positive patients.

In Japan, Ishii et al. [38] analyzed the clinical impact of amyloid PET with [^{11}C]PiB on diagnosis in 66 patients with suspected early-onset dementia (<65 years) due to AD or other neurodegenerative diseases. Following disclosure of PET results, there was a change in diagnosis in 41% of patients and increased diagnostic confidence in 76% of patients. Diagnoses were revised in almost all cases where the PET result was inconsistent with the pre-PET working diagnosis. Based on comparisons with a separate late-onset dementia cohort (diagnostic revision

in 24% of patients), the authors suggested that amyloid PET could potentially have a greater clinical impact in early-onset than late-onset dementia [38]. [18F]Flutemetamol has been shown to perform similarly to [11C]PiB in subjects with AD, MCI, and in healthy volunteers [41, 42]. Quantitative comparisons have shown high correlation between Centiloid-scaled [18F]flutemetamol PET and [11C]PiB PET reference data, further establishing the comparability of results between these two tracers of similar chemical structure [42].

A patient-level meta-analysis quantified the impact of amyloid imaging on diagnostic change, diagnostic confidence, and management across 12 studies in cognitively impaired patients [23]. In almost a third of 1,142 cases analyzed, diagnoses were changed after amyloid PET data were made available. Moreover, diagnostic confidence increased for 62.1% of 870 patients in whom this measure of utility was analyzed [23]. However, analysis of time-related diagnostic changes in the absence of amyloid status suggested that the diagnosis tended to remain unchanged over time (at least 3 months). In contrast, for matched subjects with PET results disclosed, significant diagnostic change was seen when the pre-PET diagnosis was inconsistent with the PET result, whether amyloid-positive or -negative [43].

Taken together, the findings across studies with [11C]PiB, [18F]florbetaben, [18F]florbetapir, and [18F]flutemetamol suggest that amyloid imaging leads to diagnostic revision in approximately one third of cases, and increases diagnostic confidence in over half of cases, especially when the PET result is positive. In the clinical cohort reported in this paper, 34% of diagnoses were revised following disclosure of PET results, which is comparable with previous reports and within the observed range of 19–67% for different patient populations [34–39]. Apart from descriptive evidence (from discussions with the referring physicians), it was not possible in this study to analyze systematically the impact of amyloid imaging on patient management. However, amyloid PET led to change in diagnosis for at least 1 in 3 subjects, and this would be expected to affect therapy, care plans and/or referrals for additional investigations as well as aiding post diagnosis discussions on clinical prognosis.

In summary, the results from this site analysis indicate in a Japanese clinical population that [18F]flutemetamol is safe and well tolerated and that the rate of diagnostic change is comparable to that observed in other regions of the world.

Limitations

The utility of [18F]flutemetamol PET in terms of its short term impact on the physician's working diagnosis for each subject (change from pre-scan to post-scan) was assessed. Diagnostic confidence was adopted as another measure of impact on clinical decision-making, though it is acknowledged that this measure is subjective and dependent on individual physicians' level of expertise. It is also recognized that the number of cases in this report is small and from a single site and therefore the average change of an approximate 20% rise in confidence after the scan is the most meaningful metric. Examination of the change in confidence of diagnosis after either a negative or positive scan, or whether the diagnosis is changed or remains would benefit from a larger sample size and more physicians contributing data.

Long-term follow-up to examine diagnosis and disease trajectories was beyond the scope of this report, as were analyses of diagnostic impact in categories defined based on neurocognitive or clinical assessments, or other AD biomarkers.

At present, visual interpretation is the standard method for amyloid PET assessment, but studies have shown close correlation between visual assessment and quantitative imaging [44, 45] and hence there is some evidence to suggest that quantitative amyloid imaging in the future may add value in ambiguous cases or with less experienced image readers [46].

Conclusions

The diagnostic data collected as part of a post-marketing surveillance study represents initial experience in Japan with [18F]flutemetamol PET for routine investigations in a sample of patients. [18F]Flutemetamol PET showed favorable safety and had a substantial impact on cognitive diagnosis and diagnostic confidence, supporting a revision of cognitive diagnosis in 34% of patients overall, and in 46% of MCI cases, 43% of dementia cases, and 18% of subjects with suspected AD. Mean confidence in the cognitive diagnosis increased approximately 20% as a result of the amyloid PET scan, from 73% to 93% overall. This study adds to the evidence supporting the utility of amyloid PET imaging in diagnosis in situations where there is uncertainty after standard clinical diagnostic workup and is consistent with other reports from Japanese and European studies.

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CONFLICT OF INTEREST

PS and GF are full time employees of GE Healthcare (GEHC).

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