Review Article

A Review of Diagnostic Impact of Amyloid Positron Emission Tomography Imaging in Clinical Practice

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Keywords

Amyloid · Alzheimer's disease · Biomarkers · Dementia · Mild cognitive impairment · Positron emission tomography

Abstract

Background: Molecular imaging of brain amyloid for the diagnosis of Alzheimer's disease (AD) using positron emission tomography (PET) has been approved for use in clinical practice by the Food and Drug Administration (FDA) since 2012. However, the clinical utility and diagnostic impact of amyloid PET imaging remain controversial. We conducted a review of the recent studies investigating clinical utility of amyloid PET imaging with focus on changes in diagnosis, diagnostic confidence, and patient management. **Summary:** A total of 16 studies were included in the final analysis. Overall rate of changes in diagnosis after amyloid PET ranged from 9 to 68% (pooled estimate of 31%, 95% CI 23–39%). All studies reported overall increase in diagnostic confidence or diagnostic certainty after amyloid PET. Changes in patient management ranged from 37 to 87%; the most common type of change in management reported was either the initiation or discontinuation of planned AD medications. **Key Messages:** Amyloid PET imaging led to moderate to significant changes in diagnosis, diagnostic confidence, and subsequent patient management. It may be most useful in patients with high level of diagnostic uncertainty even after the completing the standard workup.

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Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by gradual cognitive decline which progressively worsens over time. AD is the most common form of dementia in the US which is estimated to affect 5.5 million individuals [1] and is also the sixth leading cause of mortality in the US [1, 2]. Despite the increased incidence and mortality associated with AD, there is still no effective disease-modifying treatment available. Therefore, there has been increased interest in interventions that target earlier stages of AD [3] such as preclinical or mild cognitive impairment (MCI) stages. However, accurate diagnosis of AD in the earlier stages still remains a challenging task for physicians. AD biomarkers have become an integral part of clinical trials as they are useful in identifying individuals who may benefit most from a potential therapeutic intervention. In addition, since the publication of the National Institute on Aging-Alzheimer's Association (NIA/AA) working group's recommendations to incorporate biomarkers to improve diagnostic confidence [4], there have been additional efforts to integrate biomarkers into clinical practice.

Various biomarkers which target different AD stages and pathological processes have been developed over the past years. Currently, there are two major types of biomarkers: fluid-based biomarkers and imaging biomarkers. Examples of fluid-based biomarkers include cerebrospinal fluid (CSF) measures of amyloid-beta as well as total tau and phosphorylated tau; these biomarkers represent two pathological hallmarks of AD, amyloid plaques and neurofibrillary tangles, respectively. Imaging biomarkers include magnetic resonance imaging (MRI) examining brain structure, fluoro-deoxy-glucose positron emission tomography (FDG-PET) measuring the rate of glucose uptake in cortical neurons and glial cells, and more recently amyloid PET which measures the level of amyloid burden in the brain [5].

The first amyloid PET tracer to be widely studied in humans is a ^{11}C -Pittsburgh compound B (PiB) which has been well-validated for quantifying the brain amyloid burden and has been used in clinical research since 2004 [6, 7]. However, the short half-life (20 min) of ^{11}C limited its use in routine clinical settings [8]. This shortcoming has been addressed by ^{18}F -labeled radiotracers with a longer half-life (110 min). Several ^{18}F amyloid ligands have been developed, including ^{18}F -florbetapir (AmyvidTM), ^{18}F -flutemetamol (VizamylTM), ^3F -PiB or GE-067, ^{18}F -florbetaben (NeuraceqTM; also called BAY94–9172 or AV-1), and ^{18}F -NAV4694 (formerly AZD4694) [9]. At the present time, ^{18}F -labeled ligands ^{18}F -florbetapir, ^{18}F -flutemetamol, and ^{18}F -florbetaben have been approved for use in clinical settings by the US Food and Drug Administration (FDA) [10].

The appropriate use criteria (AUC), established by the Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging with a group of imaging and dementia specialists, is a set of criteria for clinical scenarios in which the use of amyloid PET would be most appropriate [11]. The three clinical indications for the use of amyloid PET imaging outlined by AUC include the following: (1) patients with progressive MCI in which clinical uncertainty exists and the patient would benefit from greater certainty; (2) patients with dementia syndrome suggestive of AD, but with an atypical presentation or suspected mixed etiology; and (3) patients with early-onset progressive cognitive decline. However, these criteria limited the use of amyloid PET to cases involving a significant clinical uncertainty, assuming that amyloid PET would be of less added value in patients with typical AD. A major issue with amyloid imaging is whether there is sufficient evidence for the clinical utility and cost-effectiveness of amyloid PET for diagnosis or treatment of dementia or neurodegenerative disease. Due to this reason, the Centers for Medicare and Medicaid Services (CMS) does not currently reimburse amyloid PET for Medicare beneficiaries [12].

In response to this decision of by CMS in 2013, a 4-year, large-scale study called "Imaging Dementia-Evidence for Amyloid Scanning (IDEAS)" was initiated by the Alzheimer's Associ-

ation and other interested stakeholders including the American College of Radiology (ACR). The aim of the IDEAS study, which was approved by the CMS in 2015, is to compile evidence on the utility and clinical impact of amyloid PET in diagnosis, diagnostic confidence, and patient management of cognitively impaired patients with a diagnostic uncertainty for those who meet the AUC. IDEAS study started enrollment in February of 2016, and completed enrollment of 18,488 Medicare beneficiaries older than 65 years of age in December 2017 [13]. The evidence gained will most likely impact on future insurance reimbursement of amyloid PET.

The goal of this review is to examine published data reflecting the clinical utility of amyloid PET with the most widely investigated radiotracer ^{11}C -PiB and the three FDA-approved ^{18}F -labeled ligands (^{18}F -florbetaben, ^{18}F -flutemetamol, and ^{18}F -florbetapir). This review will focus on the utility of amyloid PET for clinical outcomes including diagnostic decision making process (changes in diagnosis after the scan and diagnostic confidence) as well as how scan results change the clinical management of patients. This review will take a broader perspective of amyloid PET use, including studies that examined amyloid PET in different countries, in individuals who are younger (<65 years of age) as well as in those who may not meet the AUC.

Methods

Search Strategy and Study Selection

Relevant studies were identified through electronic searches, which were performed in PubMed, EMBASE, and SCOPUS, for eligible studies published from January 2012 through May 2018. The search strategy was performed with a combination of terms for titles, abstracts, and keywords (see online suppl. Table e-1; for all online suppl. material, see www.karger.com/doi/10.1159/000492151). The title and abstract of each article were initially screened by Y.K., and the full texts were reviewed for eligibility criteria by two reviewers (Y.K. and E.O.). If there were disagreements regarding eligibility, consensus was derived by discussion. The inclusion criteria of this study were as follows: (1) studies that used amyloid-PET as part of a diagnostic workup; (2) studies that included ≥ 10 subjects; (3) outcome measures included changes in diagnosis, diagnostic confidence, and/or patient management; (4) studies that were published as peer-reviewed journal articles. Studies were excluded if the studies were (1) not written in English language, (2) did not include data on clinical utility of amyloid-PET, (3) nonhuman studies. Flow diagram of the search strategy and reasons for exclusion are listed on online Supplementary e-Figure 1. Reference lists of retrieved articles were also screened to ensure all relevant studies were included.

Data Collection and Statistics

Data collection was performed by two reviewers (Y.K. and E.O.) using a data extraction form specifically designed for the study. Extracted data included author, year, participant characteristics, information on diagnostic procedure, and changes in diagnosis, diagnostic confidence, and patient management. For change in diagnosis, a meta-analysis was performed to fit a random-effects model with a random intercept for study, resulting in an estimate that accounts for both the varying size of each study and any possible correlation among observations within studies.

Results

Search Results

Literature search yielded 805 titles and abstracts (see online suppl. e-Fig. 1). After removing duplicates, a total of 644 titles and abstracts were retrieved and further reviewed for eligibility. A total of 16 studies were included in this review after eliminating articles that did not meet inclusion/exclusion criteria.

Study Characteristics

Table 1 shows the characteristics and the main findings of the included studies. Five studies were conducted in the US [7, 14, 15], 2 studies in the UK [16, 17], 2 in Netherlands [18, 19], and 1 each in Italy [10], Canada [20], France [21], and Denmark [22]. Two studies were multicenter studies with one study conducted in Australia, Germany, Japan, Switzerland, and USA [23], and the other in France, Italy, and USA [24]. ^{18}F radiotracers (^{18}F -florbetapir, ^{18}F -florbetaben, ^{18}F -flutemetamol, and ^{18}F -NAV4694) were used in 13 out of 16 studies (Table 1), and the remaining 3 studies used ^{11}C -PiB as the study ligand (Table 2). Amyloid scan results were interpreted visually in all studies; 2 studies used both visual and quantitative interpretation methods with the mean standard uptake value ratios of 1.17 [14] and 1.50 [20] as the quantitative cutoff for amyloid positivity (Table 3).

Change in Diagnosis

The overall rate of the change in prescan to postscan diagnosis ranged from 9 to 68% (pooled estimate of 31%, 95% CI 23–39%). In cases where prescan diagnosis was AD, the rate of change in diagnosis ranged from 13 to 37% [10, 15, 18–20, 25, 26]. When prescan diagnosis was non-AD etiology, diagnostic change ranged from 14 to 62% [10, 18–20, 26]. Changes in diagnosis were made in up to 66% of the cases for those with prescan diagnosis of uncertain or indeterminate etiology [22, 25, 26]. In 3 studies that examined diagnostic change in MCI, very few diagnostic changes were made after the disclosure of amyloid PET results [15, 16, 18, 25].

Two studies categorized individuals by those who met the AUC and those who did not. One study reported significantly higher rate of diagnostic change in the AUC group compared to the non-AUC group (62 vs. 45%, $p = 0.01$) [27]. Similarly, another study reported higher rate of diagnostic change in the AUC group compared to the non-AUC group (53 vs. 23%), but this difference was not statistically significant [14]. In cases where the amyloid-PET scans were positive, the rate of change in diagnosis ranged from 11 to 52% [7, 19, 22, 26]. In cases where the amyloid-PET scans were negative, the rate of change in diagnosis ranged from 7 to 57% [7, 19, 22, 26]. In 90–99% of those with amyloid-positive scans, the diagnosis of AD etiology was finalized, and 87–99% of those with amyloid-negative scans received the final diagnosis other than AD etiology [10, 26]. Those who obtained negative amyloid PET scan with previous diagnosis of AD were likely to have a diagnostic change to other disorders including dementia with Lewy bodies, corticobasal degeneration, cerebrovascular dementia (CVD), and frontotemporal lobar degeneration, depression, or dementia due to undetermined etiology [18, 25]. The majority of patients with previous clinical diagnosis of non-AD with positive scan were given postscan diagnosis of AD [10] (Table 1).

Change in Diagnostic Confidence

Change in diagnostic confidence was also examined in 10 studies, and all reported overall increase in diagnostic confidence or diagnostic certainty following disclosure of PET imaging [17–23, 25]. In a subset the study population, diagnostic confidence decreased when diagnosis changed from prescan diagnosis of AD to non-AD after a negative amyloid-PET [10, 19, 23] (Table 1).

Change in Patient Management and Treatment

Overall change in patient management ranged from 37 to 87% [16, 19–21, 24, 26, 27]. The most common type of change in management was either the initiation or discontinuation of planned AD medication such as memantine or cholinesterase inhibitors which ranged from 20 to 60% of the overall study populations [7, 10, 16, 19, 21, 26, 27]. Other types of management changes included referral to clinical trials, AD genetic testing [17], additional diagnostic tests

Table 1. Utility of amyloid positron emission tomography (PET) scans in clinical settings (¹⁸F radiopharmaceuticals)

First author [Ref.], year	PET ligands	Settings	Subjects	Outcome measures	Major findings
<i>F18 radioligand</i> Schipke [23], 2012	¹⁸ F-florbetaben	Multicenter (Australia, Germany, Japan, Switzerland, USA) 2010–2011	Total <i>n</i> = 201 Age: NR Prescan diagnosis: AD (<i>n</i> = 121) Controls (<i>n</i> = 80)	Changes in (1) diagnostic confidence	(1) Changes in diagnostic confidence: Prescan dx of AD: increased in 77/121 (78%) overall Prescan dx of control: increased in 24/80 (30%) overall
Grundman [26], 2013	¹⁸ F-florbetapir	USA 19 clinical centers 2011–2012	Total <i>n</i> = 229 Age, mean (SD): 74.1 (8.1) Prescan diagnosis: AD (<i>n</i> = 86) Non-AD (<i>n</i> = 21) Indeterminate (<i>n</i> = 122)	Changes in (1) diagnosis (2) diagnostic confidence (3) management	(1) Changes in diagnosis: 125/229 (54.6%) [95% CI, 48.1–60.9%] 32/86 (37.2%) in prescan dx of AD 13/21 (61.9%) in prescan dx of non-AD 80/122 (65.6%) in prescan dx of indeterminate (2) Changes in diagnostic confidence: 21.6% increase [95% CI, 18.3–24.8%], <i>p</i> < 0.0001 (3) Overall changes in management (≥1 change): 199/229 (86.9%) [95% CI, 81.9–90.7%] 71/229 (31.0%) changes in AD medication 17/229 (7.4%) changes in psychiatric medication 37/229 (16.2%) changes in planned referral for participation in a clinical trial 29/119 (24.4%) decrease in planned structural imaging (analyzed in a subset of patients)
Mitsis [15], 2014	¹⁸ F-florbetapir	USA Urban dementia center	Total <i>n</i> = 30 Age, mean (range): 71.7 (50–89) Prescan diagnosis: AD (<i>n</i> = 12); MCI (<i>n</i> = 1) Other (<i>n</i> = 17)	Changes in (1) diagnosis (2) diagnostic confidence	(1) Changes in diagnosis: 10/30 (33.3%) 1/12 (8.3%) in prescan dx of AD 0/1 (61.9%) in prescan dx of MCI (2) Clarification of diagnosis: 9/30 (30%)
Grundman [27], 2016 ^a	¹⁸ F-florbetapir	USA 19 clinical centers 2011–2012	Total <i>n</i> = 229 Age, mean (SD): 74.1 (8.1) AUC-like (<i>n</i> = 125) Non-AUC (<i>n</i> = 104)	Changes in (1) diagnosis (2) management	(1) Changes in diagnosis: 125/229 (54.6%) 78/125 (62%) (AUC-like) vs. 47/104 (45%) (non-AUC), <i>p</i> = 0.01 (2) Overall changes in management: 88.0% (AUC-like) vs. 85.6% (non-AUC), <i>p</i> = 0.69 25% (AUC-like) vs. 13% (non-AUC) changes in removal of AD medication after a negative scan 25% (AUC-like) vs. 20% (non-AUC) changes in neuropsychological testing 16% (AUC-like) vs. 12% (non-AUC) changes in planned brain structural imaging 13% (AUC-like) vs. 8% (non-AUC) changes in planned lumbar puncture

Table 1 (continued)

First author [Ref.], year	PET ligands	Settings	Subjects	Outcome measures	Major findings
Boccardi [10], 2016	¹⁸ F-florbetapir	Italy 18 memory clinics 2013–2014	Total <i>n</i> = 228 Age, mean (SD): 70.5 (7) Prescan diagnosis: AD (<i>n</i> = 65) Non-AD (<i>n</i> = 63)	Changes in (1) diagnosis (2) diagnostic confidence (3) management	(1) Changes in diagnosis: 62/228 (27.2%) 46/165 (27.9%) in prescan dx of AD 16/63 (25.4%) in prescan dx of non-AD (2) Changes in diagnostic confidence: 10.7% increase (AD to AD); 43.2% increase (non-AD to AD); 48.7% decrease (AD to non-AD); 7.9% decrease (non-AD to non-AD) (all changes – <i>p</i> < 0.01) (3) Changes in management: 61/93 (65.6%) started cognition-specific medications in positive amyloid-PET 6/18 (33.3%) discontinued drugs in negative amyloid-PET
Apostolova [14], 2016	¹⁸ F-florbetapir	USA University clinic Before 12/2014	Total <i>n</i> = 53 Age, mean (SD) Early-onset (age at onset <65 years) (<i>n</i> = 24): 58.9 (4.9) Late-onset (age at onset ≥65 years) (<i>n</i> = 28): 79.4 (5.7) AUC-consistent (<i>n</i> = 40) AUC-inconsistent (<i>n</i> = 13)	Changes in (1) diagnosis (2) management	(1) Changes in diagnosis: 4/24 (17%) in early-onset vs. 12/28 (43%) in late- onset, <i>p</i> = 0.04 8/15 (53%) in AUC-consistent, late-onset; 3/13 (23%) in AUC-inconsistent, late-onset, <i>p</i> = 0.1 (2) Changes in management: 19/24 (79%) in early-onset vs. 13/28 (48%) in late- onset, <i>p</i> = 0.02 6 or 7/15 (43%) in AUC-consistent, late-onset vs. 10/13 (77%) in AUC-inconsistent, late-onset, <i>p</i> = 0.07
Weston [17], 2016	¹⁸ F-florbetapir	UK Cognitive disorders clinic	Total <i>n</i> = 20 Age, mean (SD): 65.5 (7.6) Prescan diagnosis: AD (<i>n</i> = 13) Non-AD (<i>n</i> = 7)	Change in (1) diagnosis (2) diagnostic confidence (3) management	(1) Changes in diagnosis: 7/20 (35%) 1/13 (7.7%) in prescan dx of AD 6/7 (85.7%) in prescan dx of non-AD (2) Changes in diagnostic confidence Diagnostic certainty increased from 68 ± 16% to 84 ± 14% (3) Overall changes in management: 8/20 (40%) 5/20 (25.0 %) changes in AD medication 2/20 (10.0 %) changes in AD genetic testing (added)
Bensaïdane [20], 2016	¹⁸ F-NAV4694	Canada Tertiary memory clinic 2013–2015	Total <i>n</i> = 28 Age, mean (SD): 59.3 (5.8) Prescan diagnosis: AD (<i>n</i> = 16) Non-AD (<i>n</i> = 12)	Changes in (1) diagnosis (2) diagnostic confidence (3) management	(1) Changes in diagnosis: 9/28 (32%) 5/16 (31.3%) in prescan dx of AD 4/12 (33.3%) in prescan dx of AD (2) Change in diagnostic confidence: 44% increase <i>p</i> < 0.05 (3) Overall changes in management: 22/28 (78.6%) 11/28 (39.3%) change in medication 13/28 (46.4%) change in care plan

Table 1 (continued)

First author [Ref.], year	PET ligands	Settings	Subjects	Outcome measures	Major findings
Brendel [22], 2017	¹⁸ F-florbetaben (after FDG-PET)	Germany University hospital 2012–2015	Total <i>n</i> = 107 Age, mean (SD): 69.4 (9.7) Pre-amyloid PET/post- FDG-PET diagnosis: AD (<i>n</i> = 43) FTLD (<i>n</i> = 12) non-AD/ non-FTLD/not specified MCI (<i>n</i> = 25) non-AD/non-FTLD/not specified dementia (<i>n</i> = 25)	Changes in (1) diagnosis (2) diagnostic confidence	(1) Changes in diagnosis: 30/107 (28%) (from prior diagnosis after FDG-PET) (2) Diagnostic confidence: 89/107 (83%) final diagnosis reached among formerly uncertain cases after FDG-PET
Carswell [16], 2017	¹⁸ F-florbetapir	UK Memory clinic 2013–2016	Total <i>n</i> = 100 Age, median (range): 66.7 (44.5–88.0) AD (<i>n</i> = 56) Non-AD (<i>n</i> = 11) MCI (<i>n</i> = 22) MCI-AD (<i>n</i> = 9) SCI (<i>n</i> = 2)	Changes in (1) diagnosis (2) management	(1) Changes in diagnosis: 30/96 ^b (31.3%) (2) Overall change in management: 42/90 (46.7%) 24/90 (26.6%) changes in AD medication
Zwan [19], 2017	¹⁸ F-flutemetamol	Netherlands Memory clinic	Total <i>n</i> = 211 Age, mean (SD): 62 (6) Prescan diagnosis: AD (<i>n</i> = 144) FTD (<i>n</i> = 28) OD (<i>n</i> = 19) NN (<i>n</i> = 20)	Changes in (1) diagnosis (2) diagnostic confidence (3) management	(1) Changes in diagnosis: 41/211 (19%) 26/144 (18.1%) in prescan dx of AD 4/28 (14.3%) in prescan dx of FTD 2/19 (11%) in prescan dx of OD 9/20 (45%) in prescan dx of NN (2) Changes in diagnostic confidence: Increased in 183/211 (87%) patients Overall diagnostic confidence increased from 69±12% to 88±15%, <i>p</i> < 0.001 (3) Changes in management: 79/211 (37%) ^c 51/211 (24.2%) changes in AD medication 23/211 (10.9 %) changes in care planning 22/211 (10.4%) changes in ancillary investigations

Table 1 (continued)

First author [Ref.], year	PET ligands	Settings	Subjects	Outcome measures	Major findings
Pontecorvo [24], 2017	¹⁸ F-florbetapir	France, Italy, USA (60 centers)	Total <i>n</i> = 618 ^d Age, mean (SD): 72.9 (8.1) Prescan diagnosis: AD (<i>n</i> = 464) Indeterminate (<i>n</i> = 43) Non-AD (<i>n</i> = 111)	Changes in (1) diagnosis (2) diagnostic confidence (3) management (all outcomes are at 3-month follow-up time)	(1) Changes in diagnosis: 98/301 (32.6%) in immediate feedback group (IFG) vs. 19/299 (6.4%) in delayed feedback group (DFG), <i>p</i> = 0.0001 (2) Changes in diagnostic confidence Increased 20% in IFG vs. 1% in DFG, <i>p</i> < 0.001 (3) Changes in management: 204/308 (68%) in IFG vs. 166/310 (55.5%) in DFG, <i>p</i> < 0.0001 ^e 107/300 (35.7%) in IFG vs. 66/299 (22.1%) in DFG for changes in AD medication, <i>p</i> < 0.001 90/300 (30.7%) in IFG vs. 70/299 (23.4%) in DFG for changes in referral to specialist
Ceccaldi [21], 2018	¹⁸ F-florbetaben	France Tertiary memory clinics (18 clinics)	Total <i>n</i> = 205 Age, mean: 70.9 (9.7) Prescan diagnosis: AD (<i>n</i> = 148) FTLD (<i>n</i> = 14) DLB (<i>n</i> = 7) Other (<i>n</i> = 36)	Changes in (1) diagnosis (2) diagnostic confidence (3) management	(1) Change in diagnosis: 137/205 (66.8%) [95% CI, 59.9–73.2%] (2) Change in diagnostic confidence: increased in 167/203 (82%) [95% CI, 75.5–86.5%] (3) Change in management: 164/205 (80%) [95% CI, 73.9–85.2%] 79/205 (38.5%) changes in medication 17/205 (8%) changes in diagnostic tests (added) 16/205 (8%) changes in specialist referral 60/205 (29%) changes in counseling 162/205 (79%) other

AD, Alzheimer's disease; AUC, appropriate use criteria; CI, confidence interval; dx, diagnosis; FDG, fluorodeoxyglucose; FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; MCI, mild cognitive impairment; NN, nonneurodegenerative diagnosis; NR, not reported; OD, other dementia diagnosis; SCI, subjective cognitive impairment; SD, standard deviation. ^a Same study as Grundman et al. [26]. ^b Four patients did not have documented postscan diagnosis. ^c Changes in management occurred in 79 patients. Some patients had more than one change in management. ^d Randomized (1:1) to immediate or delayed feedback arms (control). ^e The change in patient management at month 3 compared to planned management recorded at baseline in ≥1 of the items in the composite index.

Table 2. Utility of amyloid positron emission tomography (PET) scans in clinical settings (¹¹C-Pittsburg compound-B)

First author [Ref.], year	PET ligands	Settings	Subjects	Outcome measures	Major findings
¹¹ C-PiB					
Frederiksen [25], 2012	¹¹ C-PiB	Denmark Memory clinic 2008–2011	Total <i>n</i> = 57 Age, mean (SD): 65.7 (9) AD (<i>n</i> = 16) Prodromal AD (<i>n</i> = 3) aMCI (<i>n</i> = 1) SCI (<i>n</i> = 3) Undetermined (<i>n</i> = 13) Depression (<i>n</i> = 6) Other (<i>n</i> = 15)	Changes in (1) diagnosis (2) diagnostic confidence	(1) Change in diagnosis: 13/57 (23%) 2/16 (12.5%) in prescan dx of AD 1/3 (33.3%) in prescan dx of prodromal AD 0/3 (0.0%) in prescan dx of aMCI 1/3 (33.3%) in prescan dx of SCI 7/13 (53.8%) in prescan dx of undetermined etiology 1/6 (16.7%) in prescan dx of depression 1/15 (6.7%) in prescan dx in the other (2) Changes in diagnostic confidence: increased in 28/57 (49%) of the patients
Ossenkoppele [18], 2013	¹¹ C-PiB/FDG	Netherlands Hospital 2009–2011	Total <i>n</i> = 154 Age, mean (SD): AD (<i>n</i> = 66): 64 (7) MCI (<i>n</i> = 30): 64 (9) SMC (<i>n</i> = 15): 64 (6) FTD (<i>n</i> = 18): 67 (6) Dementia-other (<i>n</i> = 10): 65 (10) DLB (<i>n</i> = 5): 65 (7) Psychiatry (<i>n</i> = 6): 56 (7) Neurology-other (<i>n</i> = 4): 59 (9)	Changes in (1) diagnosis (2) diagnostic confidence	(1) Change in diagnosis: 35/154 (23%) 22/66 (33%) in prescan dx of AD 0/30 (0 %) in prescan dx of MCI 0/15 (0 %) in prescan dx of SMC 7/18 (39%) in prescan dx of FTD 2/10 (20%) in prescan dx of dementia-other 1/5 (20%) in prescan dx of DLB 1/6 (16.7%) in prescan dx of psychiatry 1/4 (25%) in prescan dx of neurology-other (2) Change in diagnostic confidence: Overall increase from 71±17% to 87±16% after PET (<i>p</i> < 0.001)
Sanchez-Juan [7], 2014 ^a	¹¹ C-PiB/FDG	USA Memory and Aging Center 2005–2011	Total <i>n</i> = 140 Age, mean (SD): 65.0 (8.2) AD (<i>n</i> = 25) MCI (<i>n</i> = 10) FTD (<i>n</i> = 27) Other (<i>n</i> = 78)	Changes in (1) diagnosis (2) management	(1) Change in diagnosis: 13/140 patients (9%) 6/64 (9.4%) in prescan dx of Aβ category ^b 7/76 (9.2%) in prescan dx of non-Aβ category (2) Changes in management: AChE-I change in those with prescan dx of non-Aβ syndrome 8/60 (13%) in PiB concordant group 6/14 (43%) in PiB discordant group ^c (<i>p</i> = 0.02)

AChE-I, acetylcholinesterase inhibitor; AD, Alzheimer's disease; aMCI, amnesic mild cognitive impairment; CBS, corticobasal syndrome; DLB, dementia with Lewy bodies; FDG, fluorodeoxyglucose; FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; HC, healthy control; MCI, mild cognitive impairment; NA-MCI, non-amnesic mild cognitive impairment; NN, non-neurodegenerative diagnosis; OD, other dementia diagnosis; PiB, Pittsburgh compound B; posAD, possible AD; PPA, primary progressive aphasia; proAD, probable AD; SCI, subjective cognitive impairment; SD, standard deviation; SMC, subjective memory complaints. ^a Although this study was conducted in a research setting, the results of amyloid-PET scans were made available to the clinicians for patient management. ^b Aβ category – typical (memory-predominant) and atypical AD including AD, PPA: logopenic variant, posterior cortical atrophy, aMCI, CBS-AD, non-Aβ category – primarily clinical variants of FTD including nonamnesic MCI, behavioral variant FTD, PPA; nonfluent variant, PPA; semantic variant, CBS-non-AD, prion disease, paraneoplastic syndrome, traumatic brain injury, psychiatric. ^c Discordance indicates discrepancy between PET reads and clinical diagnosis.

Table 3. Evaluation of amyloid-PET results

First author [Ref.], year	PET ligand	Image analysis	Qualitative assessment		Quantitative assessment		Reference region
			image analysis	interrater reliability	method	cutoff value, AUC	
Schipke [23], 2012	¹⁸ F-florbetaben	NR	NR	NR	NR	NR	NR
Grundman [26], 2013	¹⁸ F-florbetapir	visual	binary	NA	NA	NA	NR
Mitsis [15], 2014	¹⁸ F-florbetapir	visual	binary	NR	NA	NA	cerebral gray matter
Grundman [27], 2016	¹⁸ F-florbetapir	visual	binary	NA	NA	NA	NR
Bocardi [10], 2016	¹⁸ F-florbetapir	visual ^a	binary	$\kappa = 0.74$; SE, 0.042	NA	NA	NR
Apostolova [14], 2016	¹⁸ F-florbetapir	visual, quantitative	binary	NR	SUVR ^b	1.17	whole cerebellum
Weston [17], 2016	¹⁸ F-florbetapir	visual	binary	NR	NR	NR	NR
Bensaidane [20], 2016	¹⁸ F-NAV4694	visual, quantitative	binary	NR	SUVR	1.50	cerebellar cortex
Brendel [22], 2017	¹⁸ F-florbetaben	visual	binary	NR	NA	NA	NR
Carswell [16], 2017	¹⁸ F-florbetapir	visual	binary	NR	NA	NA	NR
Pontecorvo [24], 2017	¹⁸ F-florbetapir	visual	binary	NA	NA	NA	NR
Zwan [19], 2017	¹⁸ F-flutemetamol	visual	binary	NR	NA	NA	NR
Ceccaldi [21], 2017	¹⁸ F-florbetaben	visual	binary	NR	NA	NA	NR
Frederiksen [25], 2012	¹¹ C-PiB	visual	binary	NR	NA	NA	white matter
Ossenkoppele [18], 2013	¹¹ C-PiB	visual	binary	NR	NA	NA	cerebellar gray matter
Sanchez-Juan [7], 2014	¹¹ C-PiB	visual	binary	NR	NA	NA	cerebellum

AUC, area under the curve; NA, not applicable; NR, not reported; PiB, Pittsburgh compound B; SUVR, standard uptake value ratio.

^a 267 amyloid PET scans by two readers, and 15 cases read by a reference expert from the ligand manufacturer. ^b SUVR estimated in the context of the publication; 1 positive clinical read with a normal SUVR = 0.94; 5 negative clinical reads with a positive SUVR from 1.30 to 1.44 attributed to poor scan quality or possible late acquisition and brain atrophy.

[21], or starting depression treatment [16, 26]. A significant reduction in additional investigations was noted in 2 studies. One study reported 24% decrease in plans for structural imaging after amyloid pathology was confirmed by amyloid PET [26]; another study showed that the number of investigations (e.g., MRI or CT head, DaTscan or FDG-PET, CSF analysis, neuropsychological assessment, and genetic blood tests) decreased after amyloid PET became available compared to a prior time period [16].

When the AUC was applied, overall change in management was slightly higher in the AUC group compared to the non-AUC group in one study, but the difference was statistically not significant (88 vs. 86%, $p = 0.69$) [27]. Another study also did not find significant differences in change in management between the AUC and the non-AUC groups [14] (Table 1).

Discussion

The goal of this review article was to provide overview of the clinical utility of amyloid PET including diagnosis, diagnostic confidence, and patient management. The rate of change in diagnosis differed based on several factors including the patient demographics, complexity of the patient population, prescan diagnosis, and whether or not the patients met the AUC criteria. Some studies examined patients who presented with diagnostic uncertainty with

atypical presentation or early-onset features [16, 17, 26], while others examined all-comers [7, 10, 15, 18, 25]. Studies that limited the use of amyloid-PET to those with atypical presentation or early-onset features had a higher rate of change in diagnosis compared to the studies that included all-comers. The higher rate of change in diagnosis suggests that amyloid PET is more useful for patients with high level of diagnostic uncertainty even after completing the standard workup [18].

Among the studies that were included in our review, diagnostic changes were uncommon when the prescan diagnosis was MCI. However, they were based on a small number of individuals [16, 18, 25]. Most recent report from the interim analysis of the IDEAS study which had a large number of individuals with MCI diagnosis showed that changes in diagnosis were seen in a large proportion of the MCIs [28]. Additional utility of amyloid PET in MCI is reflected in the interim analysis of the IDEAS study which showed that changes in medical management were seen in 67.8% of MCI patients. Changes in medical management consisted of 47.8% change in AD drugs, 36.0% in non-AD drugs, and 23.9% changes in counseling [28].

Elevated amyloid deposition in MCI is associated with greater cognitive decline over time [29]. Despite the low rate of diagnostic change in MCI in the studies included in this review, it is important to take into consideration that amyloid PET reveals critical information for identifying individuals who are at high risk for disease progression [30]. Current AUC identifies MCI patients with clinical uncertainty as a group in which amyloid PET would be clinically useful [11], and MCI patients with high amyloid burden should be closely monitored [31].

Amyloid PET had considerable impact on change in treatment and management plan. The most common change reported was either an initiation of drug therapy with acetylcholinesterase inhibitors (AChEIs) or memantine, or discontinuation of previously prescribed medication. Currently, the existing therapeutic options are limited to symptomatic and not disease-modifying treatments [10, 32]. However, even with the lack of disease-modifying therapy for AD, amyloid PET still adds value to the management of patients by improving diagnostic confidence and clarifying diagnostic dilemmas [33]. It will help minimize misdiagnosis of patients, and also minimize adverse events due to potentially inappropriate treatment of patients as in the case of AChEI use in frontotemporal lobar degeneration patients [34–36]. Nevertheless, it is important to note that in one recent randomized control trial examining the impact of amyloid PET on patient management, AChEI use did not change significantly in subjects with negative amyloid PET [24].

Another notable change in management was the reduction of additional diagnostic tests (e.g., FDG-PET, structural imaging, neuropsychological tests). In some studies, planned structural imaging, a routine part of dementia workup, was eliminated in a substantial proportion of patients, regardless of amyloid positivity [16, 26, 27]. Removal of additional testing from the patient's management plan may in part demonstrate that clinicians viewed amyloid status as offering adequate information, especially in patients with mild cases of cognitive impairment where additional testing may not yield much more information (e.g., borderline or negative FDG-PET, psychometric testing) [26]. However, one of the studies that had autopsy results from a subgroup of patients showed that 2 patients who had positive amyloid PET had primary frontotemporal dementia pathology along with copathology of AD [7]. Therefore, more caution needs to be exercised in relying heavily on amyloid PET results in clinical diagnosis [7]. The IDEAS study may answer the question of whether revised clinical workup brought about by disclosure of amyloid PET results actually translates into a better clinical outcome [13].

Two studies extensively reviewed the impact of Appropriate Use Criteria (AUC) [14, 27]. In both studies, the rates of diagnostic change following the disclosure of amyloid PET results were reported to be higher in the AUC groups, which tended to include a larger number of

patients with diagnosis of atypical or non-AD etiology compared to the non-AUC groups. However, in terms of patient management the overall rate of change in management was comparable or even higher in the non-AUC group compared to AUC group in both studies [14, 27]. This may be partly due to how each study defined as change in patient management, as one of the studies included counseling about diagnosis and addressing potential safety concerns as part of the patient management [27]. These types of patient care activities would most likely apply equally to both AUC and non-AUC groups. Considering a greater incremental value of amyloid imaging in subjects with significant diagnostic uncertainty, AUC seem to be useful in determining what types of patients may benefit from amyloid PET in terms of clarifying diagnosis. Nevertheless, the high rates of change in treatment and management plans in patients who did not meet the strict definition of the criteria for AUC may imply that amyloid PET imaging may provide equally helpful piece of information for the non-AUC group of patients as well. Further examination of different categories of patient management and longitudinal outcome assessment of changes in management will inform the most effective use of amyloid PET.

The present review has several limitations. First, these are essentially studies of clinician behavior in response to amyloid PET results. Clinician bias might have affected the results due to the real-world, observational nature of these studies. Second, there are few data on clinicopathological correlations of amyloid PET with autopsy findings. Third, we did not search grey literature, such as abstracts from conferences with exception of the interim report from the IDEAS study. Given the limited number of studies included, mostly with small sample sizes, the findings should be further confirmed by large-scale and longitudinal studies to estimate the generalizable conclusion on the utility of amyloid PET. However, the strengths of this review include encompassing recent clinical studies from around the world, providing a global perspective on AD diagnosis and management in the context of the availability of amyloid PET as a diagnostic tool. In addition, whereas the IDEAS study primarily focused on Medicare beneficiaries in the US who are 65 or older and meet AUC, our review also included studies that examined the impact of amyloid-PET on a broader range of individuals including those who are younger (<65 years old) and those who did not meet AUC criteria. This broader inclusion may provide added insights into the clinical value of amyloid PET in more heterogeneous populations. As new AD biomarkers become available in the future, diagnostic pathways for AD will most likely continue to evolve.

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