Alzheimer's & Dementia 15 (2019) 1458-1467

Featured Article

Assessment of the appropriate use criteria for amyloid PET in an unselected memory clinic cohort: The ABIDE project

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Abstract

Introduction: The objective of this study was to assess the usefulness of the appropriate use criteria (AUC) for amyloid imaging in an unselected cohort.

Methods: We calculated sensitivity and specificity of appropriate use (increased confidence and management change), as defined by Amyloid Imaging Taskforce in the AUC, and other clinical utility outcomes. Furthermore, we compared differences in post–positron emission tomography diagnosis and management change between "AUC-consistent" and "AUC-inconsistent" patients.

Results: Almost half (250/507) of patients were AUC-consistent. In both AUC-consistent and AUC-inconsistent patients, post–positron emission tomography diagnosis (28%–21%) and management (32%–17%) change was substantial. The Amyloid Imaging Taskforce's definition of appropriate use occurred in 55/507 (13%) patients, detected by the AUC with a sensitivity of 93%, and a specificity of 56%. Diagnostic changes occurred independently of AUC status (sensitivity: 57%, specificity: 53%).

Discussion: The current AUC are not sufficiently able to discriminate between patients who will benefit from amyloid positron emission tomography and those who will not.

Keywords: Alzheimer's disease; Amyloid; Positron emission tomography; Appropriate use criteria; Dementia; Clinical practice

Conflict of interest: A.d.W., R.O., W.P., F.B., C.G., I.v.M., M.Z., M.Y., G.J.B., and B.N.M.v.B. report no disclosures. F.B serves as a consultant for Biogen-Idec, Janssen Alzheimer Immunotherapy, Bayer-Schering, Merck-Serono, Roche, Novartis, Genzume, and Sanofi-aventis and has received sponsoring from EU-H2020, NOW, SMSR, TEVA, Novartis, and Toshiba and serves on the editorial boards of Radiology, Brain, Neuroradiology, MSJ, and Neurology. A.A.L. is currently the principal investigator of a study sponsored by Avid. P.S. has acquired grant support (for the institution) from GE Healthcare, Danone Research, Piramal, and MERCK. In the past 2 years, he has received consultancy/speaker fees (paid to the institution) from Lilly, GE Healthcare, Novartis, Sanofi, Nutricia, Probiodrug, Biogen, Roche, Avraham, and EIP Pharma. Research programs of W.M.v.d.F. have been funded by ZonMW, NWO, EU-FP7, Alzheimer Nederland, Cardiovasculair Onderzoek Nederland, Stichting Dioraphte, Gieskes-Strijbis fonds, Boehringer Ingelheim, Piramal Imaging, Roche BV, Janssen Stellar, and Combinostics. All funding is paid to her institution.

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https://doi.org/10.1016/j.jalz.2019.07.003

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia and is characterized by accumulation of cerebral amyloid-β (Aβ) plaques and tau neurofibrillary tangles [1–3]. The advent of the positron emission tomography (PET) tracer ^{11}C-labeled Pittsburgh Compound-B enabled *in vivo* detection of fibrillary Aβ plaques [4]. Within the context of a paradigm shift from defining AD as a clinical syndrome toward a biological definition, amyloid PET is incorporated as a biomarker in the research criteria for AD [5–8].

The Food and Drug Administration (FDA) approval of ^{18}F-labeled amyloid PET ligands allowed widespread use of amyloid PET in clinical practice [9]. However, FDA approval was based on results from phase 1-3 trials in populations that do not accurately reflect the anticipated clinical use of amyloid PET. Data assessing the clinical utility of amyloid PET were not required for FDA approval, and thus not available [10]. Against this backdrop and within the context of upcoming decisions on reimbursement of amyloid PET by insurance third party payers, appropriate use criteria (AUC) for amyloid imaging were formulated to guide its clinical use [11].

The Amyloid Imaging Taskforce (AIT) that proposed the AUC emphasized that the formulated criteria were mainly based on expert opinion given the limited experience with clinical use of amyloid PET at that time. Amyloid PET was considered appropriate for use by dementia experts only and limited to cognitively impaired patients to retrieve the etiology of cognitive decline after a standard diagnostic evaluation. In addition, knowledge of amyloid status should be expected to both increase diagnostic confidence and change patient management, that is, the definition of appropriate use according to the AIT.

So far, only a few studies have evaluated the usefulness of the AUC, consistently finding high proportions of changes in diagnosis and patient management, in both patients consistent and inconsistent with the AUC [12–15]. However, studies to-date included selected patient populations, whereas a robust evaluation of AUC would require an unselected sample to begin with. In addition, it has not been assessed whether the AIT's definition of appropriate use, a combination of increased diagnostic confidence and management change, provides the best reflection of clinical benefit. We therefore evaluated the usefulness of the AUC for amyloid imaging in an unselected memory clinic cohort (1) to determine if AUC-consistent patients have greater clinical benefit from amyloid PET compared with AUC-inconsistent patients, and (2) to determine the AUC's test characteristics (e.g., sensitivity, specificity) for selecting patients with the AIT's definition of appropriate use (combination of increase in diagnostic confidence and change in patient management).

2. Methods

2.1. Patients

As part of the ABIDE (Alzheimer Biomarkers In Daily practicE) project [16], we performed a PET clinical utility study in which we offered [^{18}F]florbetaben PET to all consecutive memory clinic patients between January 2015 and December 2016 [17,18]. All patients underwent a standard diagnostic dementia evaluation consisting of medical history, informant-based history, neurological examinations, neuropsychological testing, basic laboratory testing, and MRI. Of all patients (n = 507), 234 (46%) had dementia, 114 (22%) mild cognitive impairment (MCI), and 159 (31%) subjective cognitive decline (SCD). In 252 (50%) patients, the pre-PET suspected etiology was AD, in 89 (18%) non-AD, and in 166 (32%) non-neurodegenerative (i.e., other neurological disease [such as multiple sclerosis, epilepsy, or vasculitis], psychiatry, obstructive sleep apnea syndrome, or worried well). Most patients with a nonsuspected neurodegenerative etiology had an SCD syndrome diagnosis and were considered worried well (89/166, 54%). The study was approved by all relevant institutional ethical review boards.

2.2. Diagnostic procedure

In short, clinical syndrome (dementia, MCI, or SCD), suspected etiology (AD, vascular pathology, frontotemporal dementia, Lewy body dementia, other neurodegenerative disease, or non-neurodegenerative disease), and level of diagnostic confidence in suspected etiology (visual analog scale, 0–100%) were determined during pre-PET multidisciplinary meetings. In addition, patient management in terms of (i) ancillary investigations (e.g. [^{18}F]FDG PET scan, DAT scan, genetic testing), (ii) initiation or withdrawal of AD medication (i.e. cholinesterase inhibitors and trial participation), and (iii) initiation or withdrawal of formal care was determined. After disclosure of PET results to the neurologists, the clinical syndrome, suspected underlying etiology, diagnostic confidence, and patient management were re-evaluated.

2.3. PET procedure

All procedures regarding the amyloid PET procedure using [^{18}F]florbetaben and its whole-brain visual assessment have been described in detail elsewhere [16,18].

2.4. Classification according to the AUC scheme

The appropriate use criteria were retrospectively examined by two reviewers (A.d.W. and R.O.), using a restrictive interpretation of the proposed AUC guidelines, very similar to earlier approaches by Grundman et al. and Altomare et al. [12,14]. Patients were labeled as "AUC-consistent" or "AUC-inconsistent", applying the AUC as following:

1. The AUC state that patients should present with a cognitive complaint and objectively confirmed impairment. Therefore, all patients with a syndrome

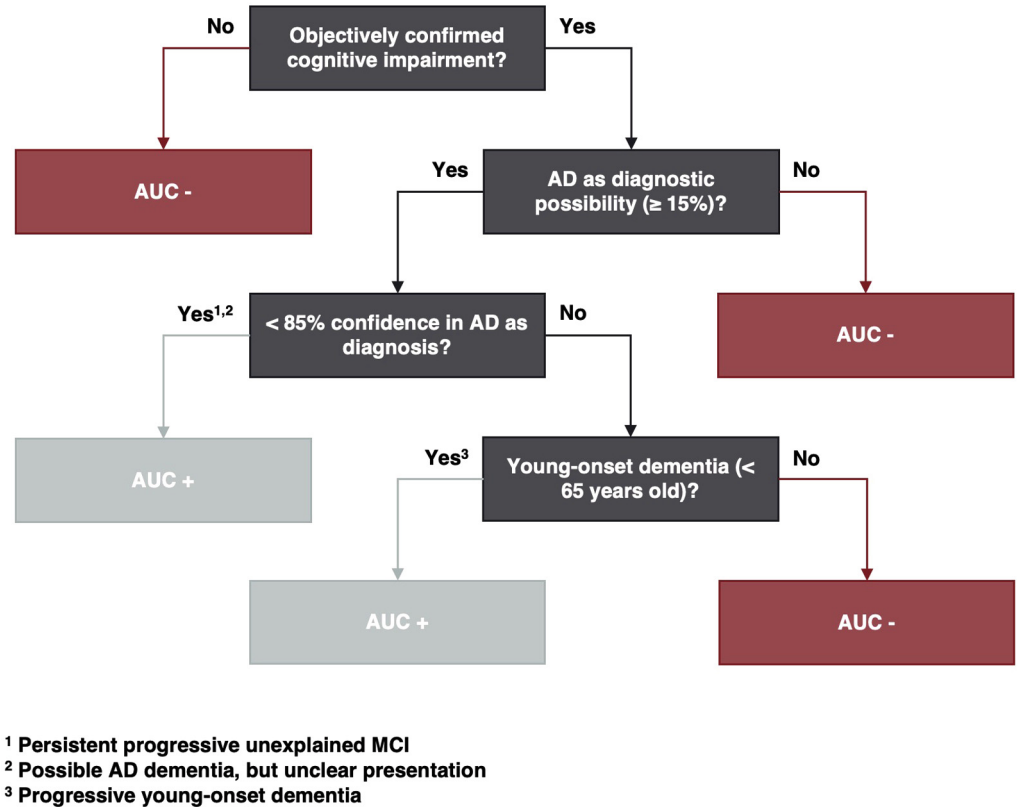

Fig. 1. Decision tree of classification of patients according to the AUC scheme. Abbreviations: AD, Alzheimer's disease; AUC, appropriate use criteria; MCI, mild cognitive impairment.

diagnosis of subjective cognitive decline were classified as AUC-inconsistent.

2. AD should be a possible diagnosis according to the AUC. Therefore, we classified all patients as AUC-inconsistent where the study neurologist a) did not suspect AD as a primary or alternative etiology or b) confidence in AD as suspected etiology was <15%.
3. There has to be uncertainty about AD as a possible diagnosis. We classified all patients with cognitive impairment with ≥85% confidence in suspected etiology of AD as AUC-inconsistent, with the exception of patients with young-onset dementia. These patients were classified as AUC-consistent according to AUC scenario (3): patients with progressive dementia and an early age at onset (<65 years).
4. The remainder of patients (with MCI and dementia) had AD as a suspected etiology (primary or alternate), and a confidence in suspected etiology ranging between 15 and 84%. Within dementia, we considered this range of diagnostic confidence to be reflecting an atypical or unclear clinical presentation. For patients with MCI to be considered AUC-consistent, self-reported symptom duration had to be > 6 months. The latter were defined as AUC-consistent and categorized according to the three AUC scenario's: (1) patients with persistent or progressive unexplained MCI, (2) patients with possible AD dementia, but unclear clinical presentation, or (3) patients with progressive dementia and an early age at onset (<65 years).

Fig. 1 shows a decision tree of the application of the criteria. The concordance between the two reviewers for AUC-consistent versus AUC-inconsistent was 98%, and discordant cases (n = 11, 2%) were resolved by consensus.

2.5. Outcome measures

Our primary outcomes measures were post-PET change in suspected etiology, increase in diagnostic confidence (≥15%), and change in patient management. First, we compared change in suspected etiology and change in patient management between AUC-consistent and AUC-inconsistent patients. We did not compare change in diagnostic confidence between these two groups, as this is an integral part of the determinant, it cannot also be evaluated as outcome. Second, we assessed test characteristics of the AUC for detecting patients with the AIT's definition of appropriate use (combination of increase in diagnostic confidence and change in patient management). In addition, we assessed the AUC's test characteristics for the individual outcome measures and their respective remaining combinations.

Table 1
Demographic and clinical characteristics according to appropriate use criteria status

Characteristic	AUC-consistent	AUC-inconsistent
n	250	257
Age	66 ± 8*	64 ± 8
Gender, female, %	100 (40)	100 (39)
Education†	5 ± 1	5 ± 1
MMSE	24 ± 4*	26 ± 4
APOE genotype, e4 carrier, %	119 (54)*	99 (40)
Syndrome diagnosis*, %		
SCD	-	159 (62)
MCI	89 (36)	25 (10)
Dementia	161 (64)	73 (28)
Primary suspected etiology*, %		
AD	184 (74)	68 (27)
non-AD	45 (18)	44 (17)
non-neurodegenerative	21 (8)	145 (56)
Appropriate use criteria, category, %		
Persistent unexplained MCI	89 (35)	-
Possible AD, unclear clinical presentation	82 (33)	-
Young-onset dementia	79 (32)	-

NOTE. Data are presented as mean ± SD or n (%). Differences between groups were assessed using independent samples t-tests (age, education and MMSE) and χ^2 tests (gender and *APOE* genotype, syndrome diagnosis, and primary suspected etiology). Education was unavailable for 3 patients, MMSE for 7 patients, *APOE* genotype for 39 patients, and MTA for 26 patients.

Abbreviations: AD, Alzheimer's disease; AUC, appropriate use criteria; MCI, mild cognitive impairment; MMSE, Mini–Mental State Examination; *APOE*, apolipoprotein E; SCD, subjective cognitive decline.

*$P < .005$.

†Education was rated using Verhage's classification.

2.6. Statistical analyses

We assessed differences in baseline characteristics between diagnostic groups using analysis of variance, Kruskal-Wallis tests, and Pearson χ^2 where appropriate. We used Pearson χ^2 tests to assess differences in post-PET change in etiological diagnosis and patient management between groups. For the outcome measures (change in suspected etiology, increase in diagnostic confidence (≥15%), and change in patient management) and their respective combinations, we calculated sensitivity, specificity, positive predictive value, and negative predictive value. The level of significance was set at $P < .05$.

3. Results

3.1. Demographic and clinical characteristics

We classified 250 (49%) patients as AUC-consistent and 257 (51%) as AUC-inconsistent (Table 1). When excluding patients with SCD (AUC-inconsistent by definition) the percentage of AUC-consistent patients (250/348) increased to 72%. Of AUC-consistent patients, 82 (33%) were considered to have possible AD dementia, but unclear clinical presentation, 79 (32%) had young-onset and progressive dementia, and 89 (36%) presented with persistent/progressive unexplained MCI. AUC-consistent patients were older, more often demented, had a suspected AD etiology more frequently, had a lower Mini–Mental State Examination, and were more often apolipoprotein E (*APOE*) ε4 positive than AUC-inconsistent patients (all $P < .05$). In addition, AUC-consistent patients were more often amyloid PET–positive (157/250, 63%) than AUC-inconsistent patients (85/257, 33%) ($P < .001$). Supplementary Table 1 shows the clinical impact of amyloid PET on clinical diagnosis, confidence in diagnosis, and patient management according to syndrome diagnosis and amyloid PET result.

3.2. AUC-consistent versus AUC-inconsistent patients

3.2.1. Change in suspected etiology

Table 2 shows post-PET change in suspected etiology per diagnostic group. Across all patients, there was no difference in change in suspected etiology between AUC-consistent (71/250, 28%) and AUC-inconsistent (54/257, 21%) patients ($P = .063$). In patients with suspected AD dementia, the proportion of changes in suspected etiology did not differ between AUC-consistent (25/122, 20%) and AUC-inconsistent (11/42, 26%) individuals ($P = .44$) either. By contrast, AUC-consistent patients with suspected non-AD dementia (12/39, 31% vs. 2/31, 7%; $P < .05$) or MCI (34/89, 38% vs. 4/25, 16%; $P < .05$) showed higher proportions of change in suspected etiology than AUC-inconsistent patients. In SCD patients—by definition AUC-inconsistent—suspected etiology changed in roughly one quarter (37/159, 23%).

3.2.2. Change in patient management

Overall, the proportion of patient management change was higher in AUC-consistent (80/250, 32%) than AUC-inconsistent (43/257, 17%) patients ($P < .001$). When excluding SCD patients, AUC-inconsistent by definition, there is no difference between AUC-consistent (80/250, 32%) and AUC-inconsistent (26/98, 27%) patients ($P = .365$). However, neither in patients with dementia, nor in patients with MCI, there was a difference in patient management between AUC-consistent and AUC-inconsistent patients (Table 2). Furthermore, there were no differences in the subcategories of patient management (change in ancillary investigations, medication, or formal care) between AUC-consistent and AUC-inconsistent patients. A negative amyloid PET led to most changes in ancillary investigations (35/43, 81%), mostly consisting of performing FDG-PET (n = 21), referral to a psychiatrist (n = 6), or genetic testing (n = 5). Single patients could have >1 ancillary investigations. Likewise, changes after a positive amyloid PET (8/43, 19%) mainly consisted of FDG-PET (n = 3), referral to a psychiatrist (n = 1) and genetic testing (n = 2). Changes in patient treatment were mostly due to a positive amyloid PET (71/80, 89%) and consisted of trial participation (n = 52, 65%), initiate AD drugs

Table 2
Clinical impact of amyloid PET on clinical diagnosis, confidence in diagnosis, and patient management according to clinical diagnosis and appropriate use criteria status before PET

	Dementia (n = 234)				MCI (n = 114)		SCD (n = 159)
	AD (n = 164)		Non-AD (n = 70)				
Characteristic	AUC+	AUC−	AUC+	AUC−	AUC+	AUC−	AUC−
n, %	122 (74)	42 (26)	39 (56)	31 (44)	89 (78)	25 (22)	159 (100)
Amyloid PET, positive, %	98 (80)	30 (71)	17 (44)	6 (19)	42 (47)	13 (52)	36 (23)
Change in suspected etiological diagnosis, %	25 (20)	11 (26)	12 (31)*	2 (7)*	34 (38)*	4 (16)*	37 (23)
Pre-PET diagnostic confidence (%)	79 ± 11	90 ± 4	72 ± 9	84 ± 14	69 ± 13	77 ± 20	85 ± 11
Post-PET diagnostic confidence (%)	93 ± 12	90 ± 14	87 ± 12	86 ± 12	84 ± 18	89 ± 10	91 ± 11
Change in patient management, %	45 (37)	13 (31)	8 (21)	5 (16)	27 (30)	8 (32)	17 (11)
Ancillary investigations	13 (11)	6 (14)	5 (13)	3 (10)	8 (9)	1 (4)	7 (4)
Medication (incl. trials)	36 (30)	9 (21)	3 (8)	2 (7)	19 (21)	7 (28)	4 (3)
Formal care	2 (2)	0 (0)	1 (3)	1 (3)	4 (5)	1 (4)	8 (5)

NOTE. Data are presented as mean ± SD or n (%). Differences between AUC-consistent and AUC-inconsistent patients within diagnostic groups were assessed using χ^2 tests (change in suspected etiological diagnosis and change in patient management). Differences in pre- and post-PET diagnostic confidence within each group were assessed using a paired sample test. Differences in diagnostic confidence were not assessed between groups because this was part of application of the appropriate use criteria.

Abbreviations: AD, Alzheimer's disease; AUC, appropriate use criteria; MCI, mild cognitive impairment; PET, positron emission tomography; SCD, subjective cognitive decline.

*$P < .05$.

(n = 12, 15%), and both (n = 7, 9%). A negative amyloid PET led to the following changes (9/80, 11%): stop AD drugs (n = 6, 8%), stop AD drugs and stop non-AD drugs (n = 1, 1%), stop trial participation (n = 1, 1%), and start non-AD drugs (n = 1, 1%).

3.3. AUC test characteristics for combinations of outcome measures

Fig. 2 shows the frequency of the three outcome measures (i) change in suspected etiological diagnosis, (ii) increase of diagnostic confidence, and (iii) change in patient management, and their co-occurrence. The AIT's definition of appropriate use was observed in 55/507 (11%) patients, of whom 15 had all three outcome measures. The AUC detected 51/55 (93%) of these patients (sensitivity), whereas 253/452 (56%) patients without the outcome (specificity) were AUC-inconsistent (Table 3).

Change in suspected etiology might be argued to be a relevant outcome in terms of appropriate use. Co-occurring with either increased diagnostic confidence (21/507, 4%) or patient management change (25/507, 5%), the AUC had low sensitivity (48–57%), low specificity (51–51%), very low positive predictive value (5%), but very high negative predictive value (95–97%) for detecting patients with these combinations of outcomes.

3.4. Outcome measures and patient profiles

We identified distinct patient profiles when we assessed the different combinations of outcome measures (Fig. 2) for their patient characteristics. After amyloid PET, a total of 55 patients had the AIT defined outcome of appropriate use (increased diagnostic confidence and management change), including 15 patients who were positive for all three outcome measures. Of these patients, 34/55 (62%) had a suspected AD etiology with a concordant amyloid PET result, increasing pre-PET confidence significantly from 73% ± 10 to 97% ± 3 post-PET, leading to prescription of AD drugs or trial participation (33/34, 97%).

This patient profile is in contrast with the prevalent patient characteristics in other combinations of relevant outcome measures. Patients with a change of suspected

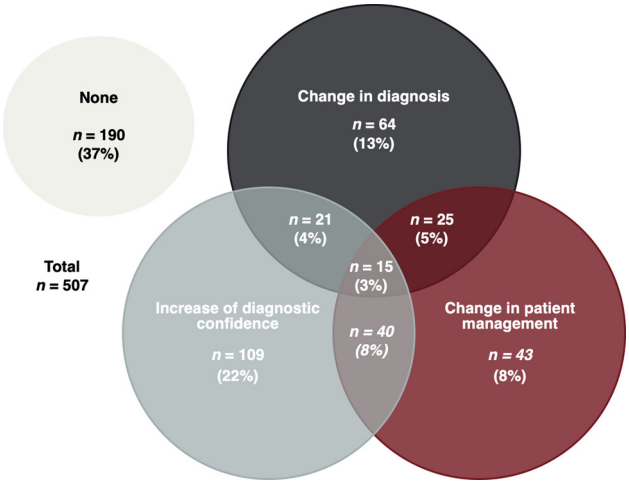

Fig. 2. Frequency of primary outcome measures and their overlap. Fig. 2 shows the frequency our primary outcome measures: post-PET (i) change in suspected etiological diagnosis, (ii) ≥15% increase of diagnostic confidence, and (iii) change in patient management. Outcome measures occurred either in isolation, or in combination with other outcome measures. The combination of increase of diagnostic confidence and change in patient management reflects the AIT's definition of appropriate use, as defined by the appropriate use criteria. Abbreviations: AIT, Amyloid Imaging Taskforce; PET, positron emission tomography.

Table 3
Sensitivity and specificity of the appropriate use criteria in selecting patients with different (combinations of) outcome measures

Outcome measure(s)	*n*, %	AUC-consistent	Sensitivity, %	Specificity, %	PPV, %	NPV, %
None	190 (37)	49				
Change in etiological diagnosis	64 (13)	33	52 (39–64)	51 (46–56)	13 (11–16)	88 (85–91)
Increase in diagnostic confidence	109 (22)	76	70 (60–78)	56 (51–61)	30 (27–34)	87 (83–90)
Change in patient management	43 (8)	17	40 (24–56)	50 (45–54)	7 (5–10)	90 (87–92)
Change in etiological diagnosis and increase in diagnostic confidence	21 (4)	12	57 (34–78)	51 (47–56)	5 (3–7)	97 (94–98)
Change in etiological diagnosis and change in patient management	25 (5)	12	48 (28–69)	51 (46–55)	5 (3–7)	95 (93–97)
Increase in diagnostic confidence and change in patient management	40 (8)	37	93 (80–98)	53 (50–59)	15 (13–17)	99 (97–100)
All outcome measures	15 (3)	14	93 (68–100)	52 (48–57)	6 (5–7)	100 (97–100)
Total	507	250 (49%)				

NOTE. Data are presented as *n* (%) or % with 95% confidence intervals.
Increase in diagnostic confidence ≥15%.
Abbreviations: AUC, appropriate use criteria; NPV, negative predictive value; PPV, positive predictive value.

etiology and increased diagnostic confidence, but no change in patient management, often had a suspected AD etiology (12/21, 57%) with low pre-PET confidence (68% ± 7), followed by a negative PET result (11/12, 92%), increasing confidence (92% ± 5) in a non-AD etiology (12/12, 100%). Finally, patients with a change in suspected etiology and management, without increased diagnostic confidence, predominantly had an AD suspected etiology (17/25, 68%) with a negative amyloid PET (17/17, 100%), which led to a decrease in diagnostic confidence from 76% (±9) to 70% (±11), resulting in additional ancillary investigations (16/17, 94%).

4. Discussion

We found that almost half of 507 patients were AUC-consistent in an unselected memory clinic cohort, whereas only 11% had both an increased diagnostic confidence and management change, thereby fulfilling the appropriate use outcome as defined by the AIT. Sensitivity of the AUC for selecting patients with the AIT's definition of appropriate use was high, but specificity was very low. When we looked at a broader array of putative clinical benefit however, we found across the spectrum of cognitive impairment, ranging from SCD to dementia, proportions of changes in diagnosis, and patient management were substantial in both AUC-consistent and AUC-inconsistent patients. In addition, the AUC "appropriate use" definition has a predisposition toward selecting AD patients with a confirmatory abnormal PET, which leads to initiating AD drugs or trial participation, whereas patients with a change of diagnosis after a conflicting PET result are largely disregarded. These results reveal that the current AUC are not able to discriminate between patients who will benefit from amyloid PET and those who will not.

According to the AUC, an amyloid PET result should be expected to increase confidence and alter patient management to be considered as "appropriate". This definition was adopted by several national PET guidelines, with the exception of the Canada Consensus Guidelines, where amyloid PET is expected to provide a more precise diagnosis and alter management [11,19–23]. Evaluating the AIT's definition of appropriate use in our cohort, we observed 55 (11%) patients with a combination of a post-PET increase in diagnostic confidence and change in patient management, of which most were identified by the AUC (93%). A remarkably homogenous sample was identified among these patients; 62% had a suspected AD etiology, followed by positive PET result (100%) increasing diagnostic confidence, resulting in a change of medication prescription or trial referral in all but one. On the contrary, the group of patients with a change of suspected etiology was less often AUC-consistent and had PET results conflicting with their suspected (mostly AD) etiology, resulting in a change of diagnosis with either increased diagnostic certainty or a decrease with subsequent additional investigations. Thus, in clinical practice amyloid PET has particular value in demonstrating the absence of AD pathology, but the group where this is most relevant is not captured by current AUC. Based on these data, "appropriate use" as defined by the AIT in the AUC does not capture the full extent of clinical benefit that amyloid PET may infer in the context of a dementia diagnosis, focusing on confidence increase and patient management, but neglecting change in diagnosis as a relevant outcome.

Previous studies investigating the usefulness of the AUC had different designs and used selected research populations [12–14]. One study selected a series of patients who underwent amyloid PET for diagnostic purposes, mostly ordered by dementia specialists [13]. Other studies used data sets from amyloid PET clinical utility studies in memory centers, and inclusion criteria were mainly based on diagnostic uncertainty of an AD diagnosis [12,14]. In contrast to the present study, patients in most of the previous studies did not undergo a standardized diagnostic workup. The proportion of patients who were

classified as AUC-consistent ranged between 55 and 75%. Changes in diagnosis, comparing AUC-consistent with AUC-inconsistent patients, was high in both groups (30–62% vs. 19–45%), as well as changes in patient management (29–88% vs. 31–86%). Recently, the first results of the U.S. Imaging Dementia–Evidence for Amyloid Scanning (IDEAS) study were published, the largest amyloid PET utility study to date, including 11.409 patients [24]. Patients were required to be AUC-consistent to be included in the study. The primary outcome, change in management, using a composite end point consisting of changes in prescription of AD drugs, non-AD drugs, or counseling, was observed in 60.2% in patients with MCI and 70.1% in patients with dementia. In addition, the secondary end point assessed change in etiologic diagnosis, which changed from AD to non-AD in 25.1%, and from non-AD to AD in 10.5% of the patients. In the present study, 49% of patients were AUC-consistent, increasing to 72% when excluding patients with SCD, who are AUC-inconsistent by definition. Changes in suspected etiology were 28% versus 21% in AUC-consistent versus AUC-inconsistent patients, whereas changes in patient management were 32% versus 17%. The difference in proportions of patient management between IDEAS and the present study could be partially due to patient selection (fulfillment of AUC was the main inclusion criterion for IDEAS, while the present study deliberately compared patients who fulfilled AUC with those who did not fulfill AUC), but an important difference with our study may be cultural; that is American versus European. In IDEAS, the number of MCI patients that receive AD drugs roughly doubles (~40% to ~80%) after a positive amyloid PET. In dementia patients, this pattern is similar, but proportionally less, because many (~60%) patients already used AD drugs before a positive amyloid, whereas a negative amyloid PET does not often result in stopping of medication either. In Europe, and particularly in the Netherlands, there is a different approach, as AD drugs, such as cholinesterase inhibitors, can only be prescribed to patients with Alzheimer's dementia because currently available literature on MCI is negative. Therefore, in our study, a positive amyloid PET in MCI resulted in start of Alzheimer medication in only three patients. All taken together, these results show that among different studies, in different countries, with different designs and patient populations, high proportions of patients are considered appropriate for undergoing amyloid PET, whereas changes in diagnosis and changes in patient management are substantial in both AUC-consistent and AUC-inconsistent patients. These results underline that the current AUC should more selectively define their criteria for patients in which use of amyloid PET is considered appropriate. However, before turning toward these criteria for patients, there is one fundamental question that needs to be solved first: how to define "appropriate use"?

In the absence of a disease-modifying therapy, PET clinical utility studies have mainly turned to three surrogate outcome measures to operationalize PET benefit: change in diagnosis, increase in diagnostic confidence, and change in patient management after amyloid PET [25,26]. So far, these measures have been indiscriminately used for patients with different suspected etiologies, in different stages of disease, whereas their significance may vary per clinical scenario. For example, for a young amnestic MCI patient, with a suspected AD etiology, a positive amyloid PET might lead to increased diagnostic confidence, in the absence of diagnostic or management change because cholinesterase inhibitor prescription is off-label [27]. It is arguable whether this change in diagnostic confidence reflects appropriate amyloid PET use, but it undeniably has a major impact on this patient's risk of clinical progression to AD dementia and thus on taking lifestyle measures and advanced care planning [28]. On the contrary, an isolated increase of diagnostic confidence after a positive PET in an older patient with atypical AD dementia has little value because the patient is already demented and amyloid PET does not predict rate of cognitive decline [29,30]. In addition, an older amnestic MCI patient with negative PET result and a subsequent isolated change of diagnosis (AD to non-AD) benefits from amyloid PET, even though diagnostic confidence decreases because this result significantly reduces the risk of developing AD dementia; whereas a similar scenario for a patient with atypical AD dementia would add limited value in the absence of a management change [31]. These cases demonstrate that depending on the individuals' demographic characteristics and clinical diagnosis, the importance of different outcome measures may vary per patient. Especially when assessing patients who are not demented (yet), changing their diagnosis or management is less relevant than the impact amyloid PET has on their prognosis. Change of prognosis is difficult to measure and can be reflected by a change in certainty or diagnosis, depending on the clinical scenario. Few studies with data on risk of developing (AD) dementia after amyloid PET have been published, but they have started to emerge [28,32–36]. In addition, we feel that clinical use of amyloid PET in patients with MCI especially should be preceded by counseling—an approach that has also been adopted in the recent guidelines on communicating MCI diagnoses with and without amyloid imaging and on the clinical use of CSF AD biomarkers [37–39]. Amyloid imaging can improve the etiological understanding of cognitive decline, or provide prognostic information, but not all patients may want this information. Therefore, counseling is necessary to help patients and their caregivers "decide whether to have the scan and to set expectations" about the possible (prognostic) implications of the PET result [37,40,41]. This is even more true for SCD patients, who currently by definition are not eligible for amyloid PET according to the appropriate use criteria, but represent a significant number of patients in memory clinics. Although these patients do not often undergo amyloid PET scans in clinical practice, this could

potentially change rapidly, as the number of trials focusing on this population increase and patients increasingly become assertive and demanding. In this respect, it is of relevance that appropriate use criteria for CSF were recently published and also include individuals with SCD [42]. Although longitudinal data on the predictive value of a positive PET in SCD patients is limited, individualized risk modeling in this population shows that information on amyloid status has particular negative predictive value in this population (i.e., no incipient decline if amyloid marker is normal) [43].

There are some limitations. First, we retrospectively determined patients' AUC status and therefore have no information on whether study neurologists expected amyloid PET to increase confidence and change patient management beforehand, which is described as a preamble for AUC appropriateness. Although this approach was also used in previous studies, this could have led to some misclassifications. Second, our operationalization of the AUC criteria was very similar to earlier studies [12,14], with one exception: contrary to Grundman et al., we regarded patients with an uncertain working diagnosis of non-AD and AD as a possible differential diagnosis as AUC-consistent. This did not affect the conclusion of our manuscript; changing their AUC classification would lead to an even poorer ability of the AUC to identify patients who benefit from amyloid PET. Third, we defined uncertainty in suspected etiology as a diagnostic confidence lower than 85% as expressed by the neurologist. This cutoff is somewhat arbitrary and was mainly adopted for the purpose of comparability with previous PET utility studies, where this cutoff was used to exclude patients with high diagnostic confidence (>85%) from the study. Fourth, the patients who participated in this tertiary memory clinic study were relatively young and often had complex clinical presentations. However, we envision that primary care should refer patients for further diagnostic workup to a memory clinic and that amyloid PET could be performed in selected cases after a comprehensive evaluation by a dementia expert in secondary or even tertiary care setting. Fifth, our routine workup is quite extensive, including neuropsychological testing, MRI, and EEG, which may have led to an underestimation of change in diagnosis and management. Nonetheless, as both AUC-consistent and AUC-inconsistent had an identical diagnostic workup including amyloid PET, we think this affected both groups evenly. Sixth, our study design deviates from common practice as we offered amyloid PET to all patients rather than diagnostically uncertain cases. This unique approach allowed us to analyze the utility of amyloid PET in patients who would not qualify for amyloid PET according to AUC, such as patients with dementia and high diagnostic confidence in AD, patients where AD is not considered as underlying cause for cognitive decline, and patients with SCD. We found that even in these AUC inconsistent patients, amyloid PET often yielded clinical benefit. Seventh, although our study clearly shows that current AUC would benefit from refinement, we do not propose modifications in the current article. We found that both appraising the AUC and proposing novel AUC is challenging, and moreover represents different research goals, which have too wide a scope to be addressed in one article. In a follow-up paper, we strive to come up with novel, data-driven criteria for appropriate use of amyloid PET. Clinical variables might include, for example, younger age, *APOE* e4 status, and cognitive test results. In addition, one might consider different ways to define appropriate use, for example, patient preferences (i.e., shared decision-making) in combination with management of expectations (what do patients aim to learn from an amyloid PET? Do they realize that the outcome of amyloid PET is a risk factor for, not a diagnosis of dementia? Would they be interested in trial participation?) Finally, we only assessed proxies of PET utility because a disease-modifying therapy is not yet available and did not have data available on other relevant outcomes, such as health care costs and quality of life. However, these aspects will be taken into account in the IDEAS study, and in the Amyloid Imaging to Prevent Alzheimer's Disease study, which started enrollment in 2018.

In this unselected tertiary memory clinic cohort, we assessed the usefulness of the current AUC for amyloid imaging. Amyloid PET had substantial impact on change in suspected etiology and change in patient management in both AUC-consistent and AUC-consistent patients. On the other hand, there were also many patients, for whom amyloid PET did not have an apparent clinical benefit. The current operationalization of the AUC focuses on identifying patients where confidence will increase, and management will change after amyloid PET, somewhat neglecting the clinical benefit of accurate alternative diagnosis—hence change in diagnosis. These findings suggest that the AUC could benefit from refinement to improve the impact of amyloid PET in daily clinical practice.

Acknowledgments

The VUmc Alzheimer Center is supported by Alzheimer Nederland and Stichting VUmc fonds. This study was performed within the framework of the Dutch ABIDE project and supported by a ZonMW-Memorabel grant (ABIDE; project No 733050201), in the context of the Dutch Deltaplan Dementie, and through a grant of Piramal Imaging (PET scan costs) to the Stichting Alzheimer & Neuropsychiatrie, Amsterdam. Research of the VUmc Alzheimer Center is part of the neurodegeneration research program of Amsterdam Neuroscience. The clinical database structure was developed with funding from Stichting Dioraphte. F.B. is supported by NIHR UCLH biomedical research center. W.v.d.F. is recipient of a grant by Stichting LSH-TKI (ABIDE-communication: LSHM16025).

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jalz.2019.07.003.

RESEARCH IN CONTEXT

1. Systematic review: Appropriate use criteria for the clinical prescription of amyloid positron emission tomography (PET) in patients with suspected Alzheimer's disease have been published, while empirical evidence on the clinical utility of amyloid PET was very sparse. In the present study, we reviewed the literature for studies assessing the ability of these appropriate use criteria to identify patients who clinically benefit from amyloid PET. We identified four studies, using selected research populations, who consistently reported high proportions of clinical benefit in both patients consistent and inconsistent with the criteria.
2. Interpretation: In this unselected memory clinic cohort, we observed two important limitations: (1) not all patients that benefit most from amyloid PET are adequately identified, and (2) for many patients consistent with the criteria, amyloid PET will not result in clinical benefit.
3. Future directions: To refine the appropriate use criteria, further research is required to identify patients who will benefit most from amyloid PET.

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