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RESEARCH ARTICLE

# Amyloid PET ordering practices in a memory disorders clinic

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## Abstract

**Introduction:** This study assessed the ordering of amyloid positron emission tomography (PET) scans in a Veterans Affairs (VA) memory disorders clinic as part of routine clinical care, with possible implications for the extent to which ordering may occur outside of the VA in the future if covered by insurance.

**Methods:** Clinical features predictive of ordering amyloid PET scans were retrospectively assessed; the percentage of patients who met appropriate use criteria were evaluated.

**Results:** Among 565 veterans, 34.9% of received an amyloid PET scan and 98.0% of these were consistent with appropriate use criteria. Patients with a PET were younger and more likely to have an initial diagnosis of Alzheimer's disease (AD). Of patients without an amyloid PET scan ordered, 64.4% would have met appropriate use criteria for amyloid PET.

**Discussion:** The majority of scans ordered were consistent with appropriate use criteria and more patients were eligible than received a scan. The current study's findings that approximately one-third of patients in a memory disorders clinic received an amyloid PET scan has implications for memory disorders clinics inside and outside of the US Veterans Health Administration.

KEYWORDS
Alzheimer's disease, amyloid PET, cognitive decline, diagnosis, biomarker

## 1 | BACKGROUND

Alzheimer's disease (AD) has historically been diagnosed clinically during life, without a definitive diagnosis possible until autopsy revealed the presence of pathognomonic amyloid plaques and neurofibrillary tangle lesions. However, in recent years there has been a re-conceptualization of AD as a biological entity involving a cascade of detectable neuropathological changes that begins in the brain 10 to 20 years before clinical symptoms and loss of function.[1–3] The biological definition of AD has reflected a shift in clinical practice toward earlier and more accurate in vivo diagnosis using biomarkers of underlying disease pathology including cerebrospinal fluid (CSF) levels of amyloid beta (A$\beta$) and tau, as well as positron emission tomography (PET) imaging.[4,5] PET advances have led to US Food and Drug Administration (FDA) approval of three amyloid tracers (florbetapir F18, florbetaben F18, and flutametamol F18) for the detection (or exclusion) of amyloid plaques in the brain to support the diagnosis of AD beginning in 2012. However, although amyloid PET studies are used frequently in

research settings, they are not yet part of standard clinical practice because Medicare and other insurers do not currently offer coverage.

Our clinical practice setting at a Veterans Affairs (VA) Medical Center is relatively unique in that we are able to regularly order amyloid PET studies as part of routine clinical care. Few prior studies have investigated the naturalistic ordering of amyloid PET scans in a memory disorders clinic.[6] The objective of the current study was to assess amyloid PET scan ordering practices in a memory disorders clinic and their adherence to Amyloid Imaging Task Force appropriate use criteria for amyloid PET ordering,[7] in an effort to determine how often clinicians might order amyloid PET imaging in memory disorders clinics if covered by insurance in the future.

**RESEARCH IN CONTEXT**

1. **Systemic Review**: The Amyloid Imaging Task Force developed appropriate use criteria based on expert opinion given the limited use of amyloid positron emission tomography (PET) in clinical practice. Few prior studies have investigated the naturalistic ordering of amyloid PET scans in a memory disorders clinic.
2. **Interpretation**: More than one-third of patients in a tertiary care memory disorders clinic received amyloid PET scans when they were readily available. Appropriate use criteria for ordering were largely adhered to. Most patients in our memory disorders population met criteria, suggesting that trained cognitive behavioral neurologists used clinical judgment when ordering amyloid PET in practice.
3. **Future Directions**: The current study reported how often amyloid PET scans might be ordered in a behavioral neurology sub-specialty memory disorders clinic.

## 2 | METHODS

The memory disorders clinic at the VA Boston Healthcare System (VA Boston) is a tertiary care clinic that receives consults from the Boston metropolitan area and the New England region. The current study includes all patients who were seen for an initial evaluation for cognitive complaints in the Memory Disorders Clinic at VA Boston from October 2016 to January 2020. The study was approved by the VA Boston Institutional Review Board for retrospective chart review and did not require informed consent.

### 2.1 | Clinical evaluation and decision to order an amyloid PET scan

As part of clinical practice, one of three cognitive behavioral neurologists complete the initial evaluation and follow-up of patients with cognitive complaints including ordering of PET scans. There are no explicit recommendations for the ordering of amyloid PET studies, but all neurologists were aware of current appropriate use criteria. All amyloid PET studies ordered are covered by the VA; the amyloid PET tracer is paid for by the VA for clinical use like other PET tracers. For the evaluation of cognitive impairment, in addition to the clinical history and exam, all patients undergo a routine workup, which includes structural brain imaging using magnetic resonance imaging (MRI) or computed tomography, routine blood work (including thyroid-stimulating hormone [TSH], vitamin B12, and vitamin D), and a cognitive battery that includes the Montreal Cognitive Assessment (MoCA),[8] Mini-Mental Status Examination (MMSE),[9] the verbal learning task from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery,[10] F-A-S Phonemic Verbal Fluency Test[11] and category fluency (including animals, fruits, and vegetables), Trail Making Test Parts A and B,[12] and the Boston Naming Test short form (BNT).[13] We also include the Geriatric Depression Scale[14] and the Geriatric Anxiety Inventory[15] to measure mood and anxiety components. After this standard evaluation, in selected cases, the neurologist performs a lumbar puncture or orders additional advanced imaging studies including amyloid PET, fluorodeoxyglucose PET (FDG-PET), or dopamine transporter scan (DaTscan), depending on the diagnostic suspicion and indication. Formal neuropsychological testing may be ordered as well. Appropriate use criteria for amyloid PET proposed by the Amyloid Imaging Task Force are considered when amyloid PET studies are ordered but it is ultimately the decision of the treating clinician to order an amyloid PET.[7]

### 2.2 | (18)F-florbetapir and $^{18}$F-florbetaben Imaging

Amyloid PET imaging at VA Boston involves an intravenous injection of 10 mCi of $^{18}$F-Florbetapir or 8.1 mCi of $^{18}$F-Florbetaben followed by a 50 to 60 minute rest period for $^{18}$F-Florbetapir and a 90 minute rest period for $^{18}$F-Florbetaben, and followed by 20 minutes of imaging of the entire brain in a single bed position using a Philips Gemini TF Big Bore PET/CT scanner. PET images are then reconstructed using iterative reconstruction ordered subset expectation maximization (OSEM) with three iterations and 33 subsets as well as low dose computed tomography (CT)–based attenuation correction.

All $^{18}$F-Florbetapir and $^{18}$F-Florbetaben PET studies were qualitatively read as amyloid positive or amyloid negative by an experienced nuclear medicine radiologist (NMR) using an inverse grayscale color map according to previously published criteria and the manufacturer's insert for both tracers.[16–18] In equivocal cases, each scan was independently read by two NMRs. Equivocal cases were defined as those in which the gray-white matter differentiation by qualitative interpretation was difficult to ascertain and were resolved by involvement of a second reader with an independent read and subsequent consensus conclusion.

The scan was also independently interpreted by the ordering cognitive behavioral neurologist as part of standard clinical practice using

the same criteria as the radiologist prior to clinical decision-making. The neurologist read was performed to place the amyloid PET results in clinical context. For example, if AD was the relevant pathology in a patient with advanced dementia, we would expect their amyloid burden to be substantial. If such a patient had small amounts of amyloid that barely met positivity criteria, we would assume that such a patient must have other pathologies also present to explain their severe clinical dementia.

## 2.3 | Clinical data collection

Clinical details were collected retrospectively from the medical record including demographic characteristics, diagnosis, medical comorbidity, disease course, cognitive testing, structural imaging, and treatment. Patients were also categorized diagnostically by clinical syndrome during the pre-amyloid PET period as subjective cognitive decline (SCD), mild cognitive impairment (MCI), or dementia. All etiological diagnoses were collected pre-amyloid PET.

MRI findings were documented using the formal MRI report from the radiologist and the assessment from the treating neurologist (visual non-quantitative readings). Presence and severity of atrophy, microvascular ischemic disease, large vessel ischemic disease, hydrocephalus, and microhemorrhages were assessed by a cognitive behavioral neurologist.

## 2.4 | Appropriate use criteria evaluation

Patients were evaluated as to whether they met amyloid PET scan appropriate use criteria based on clinical chart review of cognitive behavioral neurology attending notes and clinical evaluation. All patients with progressive dementia aged 65 and younger were counted as having met appropriate use criteria. All patients with MCI that was persistent or progressive and unexplained in etiology were counted as meeting appropriate use criteria if AD was included in the differential as well as other etiologies. Patients with core clinical criteria for possible AD in the setting of either atypical clinical course or etiologically mixed presentation with AD and other disorders in the differential were determined as meeting appropriate use criteria. Patients with classic amnestic AD dementia presentation above age 65 without any clinical concern for secondary pathologies were considered as not meeting appropriate use criteria. Patients with cognitive complains but without deficits on neuropsychological evaluation were categorized as SCD and were considered as not meeting appropriate use criteria.

## 2.5 | Statistical analysis

Analyses were performed in SPSS (Version 27). Bivariate analyses were performed using independent *t*-tests, Mann-Whitney *U* tests (for non-parametric data), and chi-square tests to evaluate demographic, neuropsychological, clinical, and structural imaging differences between patients who had an amyloid PET scan ordered as part of their workup and those in whom an amyloid PET was not ordered, correcting for multiple comparisons. Logistic regression models were used to evaluate relevant variables as potential predictors of amyloid PET ordering status. Regression models were submitted to receiver-operating characteristic (ROC) curves to calculate the sensitivity and specificity of variables of interest in predicting ordering of amyloid PET studies.

# 3 | RESULTS

From October 2016 to January 2020, at total of 570 patients were evaluated in the VA Boston memory disorders clinic for concerns of cognitive decline. Five patients were excluded from the study due to relevant clinical information not being available in the electronic medical records. A total of 565 patients were included in the analysis (Table 1). The mean age was 73.78 ± 8.93 and the cohort was predominately male (97.2%). The median duration of cognitive impairment at presentation was 2 years (interquartile range [IQR] = 1-5). Mean MoCA score at first evaluation was 20.02 ± 4.74. After the first evaluation, most patients had a presumed cognitive syndrome of MCI ($n$ = 308, 56.0%) followed by a diagnosis of dementia ($n$ = 200, 36.4%). After the initial evaluation, the most frequent suspected primary etiological diagnosis was AD (50.3%), followed by vascular dementia (9.0%) and Lewy body disease (6.9%).

Of the 565 patients in the cohort, 197 patients (34.9%) underwent amyloid PET imaging in addition to routine diagnostic workup. Of patients with a PET scan, 72 of 197 (36.5%) were positive. The appropriate use criteria were fulfilled by 193 of 197 patients (98.0%) with amyloid PET imaging and a syndromic diagnosis present. Four patients did not meet appropriate use criteria due to not having objective evidence of cognitive decline on neuropsychological testing (SCD syndrome). However, an amyloid PET scan was ordered due to patients' concerns of cognitive decline that was interfering with behavior and/or daily activities and the clinician's suspicion of AD. Among patients with MCI, 124 of 308 (or 40.2% overall) received an amyloid PET scan as part of their workup. Furthermore, five of nine patients with severe impairments defined as MoCA <10 received an amyloid PET study as part of their workup.

In the group without an amyloid PET ($n$ = 368), 16 patients (4.3%) underwent an FDG-PET and 4 patients (1.1%) underwent lumbar puncture for AD biomarkers. In the group with amyloid PET, 21 patients (10.7%) also underwent an FDG-PET: 13 patients before their amyloid PET scan and 8 patients after. One patient in the amyloid PET group had had a lumbar puncture before coming to our facility, which was deemed indeterminate.

In addition, we attempted to determine the percentage of the patients who did not undergo an amyloid PET and who would have met current appropriate use criteria. We determined that 210 of 326 patients (64.4%) without amyloid PET met appropriate use criteria. As expected, this estimate was differed significantly from rates of patients meeting appropriate use criteria within the group who received an amyloid PET, which were significantly higher (98.0%) (Table 2)

**TABLE 1** Memory disorders clinic demographic and clinical features at initial evaluation

| Characteristics | Data |
|---|---|
| Age in years, mean ± SD | 73.78 ± 8.93 |
| Male gender, *n* (%) | 549 (97.2%) |
| Years of education, mean ± SD | 13.80 ± 2.63 |
| Duration of symptoms, years | Median: 2 (IQR: 1-5) |
| MoCA initial visit, mean ± SD | 20.02 ± 4.74 |
| Family history of dementia *n* (%) | 191 (35.9%) |
| Suspected cognitive syndrome (*n* = 550), *n* (%) | |
| Unimpaired | 10 (1.8%) |
| Subjective cognitive decline | 32 (5.8%) |
| Mild cognitive impairment | 308 (56.0%) |
| Dementia | 200 (36.4%) |
| Suspected primary diagnosis (*n* = 435), *n* (%) | |
| Alzheimer's disease | 219 (50.3%) |
| Vascular | 39 (9.0%) |
| Lewy body diseases | 30 (6.9%) |
| Psychiatric disorders | 28 (6.4%) |
| BvFTD | 14 (3.2%) |
| Primary progressive aphasias | 7 (1.6%) |
| Chronic traumatic encephalopathy | 10 (2.3%) |
| Parkinson-plus syndromes | 10 (2.3%) |
| Other | 55 (12.6%) |
| Unclear | 23 (5.3%) |
| Amyloid PET completed | 197 (34.9%) |
| Indication, *n* (%) | |
| Mild cognitive impairment | 93 (47.2%) |
| Dementia with atypical clinical course or etiologically mixed | 75 (38.1%) |
| Early onset dementia | 25 (12.7%) |
| Not fulfilling AUC | 4 (2.0%) |

*n* = 565.
Values represent number (percentage) and means with standard deviation.
IQR= interquartile range; MoCA= Montreal Cognitive Assessment, AUC= appropriate use criteria; BvFTD = behavioral variant frontotemporal dementia

($p < 0.001$). Furthermore, 77% of memory clinic patients overall met appropriate use criteria.

## 3.1 | Group comparisons

We compared patient demographic, clinical, neuroimaging, and neuropsychological features between patients who had an amyloid PET scan ordered compared to those without a scan (Table 2). Patients who underwent an amyloid PET as part of their workup were on average younger and had a higher prevalence of suspected AD at initial evaluation compared to the group without amyloid PET scans. After correcting for multiple comparisons, no group difference in vascular, psychiatric, imaging, or neuropsychological measures was observed. There were trends, however, for patients who underwent an amyloid PET scan to have a higher prevalence of posttraumatic stress disorder (PTSD) as well as a higher prevalence of MCI as a syndromic diagnosis.

## 3.2 | Regression and ROC analysis

Binary logistic regressions were used to determine which clinical features were significant predictors of amyloid PET ordering status. Younger age (odds ratio [OR] 0.93, 95% confidence interval [CI] 0.88 to 0.93; $p < 0.001$) and initial clinical diagnosis of AD (OR 3.52, 95% CI 2.23 to 5.57, $p < 0.001$) were both found to be significant predictors of amyloid PET ordering. This regression was submitted to an ROC curve for analysis to determine the sensitivity and specificity of younger age and AD diagnosis as predictors of amyloid PET ordering. We found an area under the curve (AUC) of 0.78 (CI 0.73 to 0.82, $p < 0.001$).

# 4 | DISCUSSION

Overall, we found that a little more than one-third of patients in a tertiary care memory disorders clinic underwent an amyloid PET scan as part of their diagnostic workup when such scans were readily available. The predictive clinical features of an amyloid PET being ordered were younger age at presentation and presence of suspected AD diagnosis at initial visit. Appropriate use criteria for amyloid PET ordering[7] were adhered to for the vast majority of scans ordered (97.97%). In a small percentage of cases, an amyloid PET scan was ordered in a patient with a syndromic diagnosis of SCD when—despite normal performance on cognitive testing—abnormalities in behavior or function were present. Ordering amyloid PET among patients with behavioral abnormalities and SCD is in part supported by others findings that over 80% of patients with amyloid positive SCD had neuropsychiatric symptoms.[19]

The Amyloid Imaging Task Force developed appropriate use criteria based on expert opinion given the limited use of amyloid PET in clinical practice. Our memory clinic's ordering practices in a veteran population are consistent with this recommended use of amyloid PET scans at the MCI stage primarily and in younger patients with atypical presentations. Of interest, we found that a quite high percentage of patients in our memory disorders clinical population met criteria for an amyloid PET study (64.4% of those without an amyloid PET), suggesting that, in practice, trained cognitive behavioral neurologists use their clinical judgment in scan ordering, resulting in fewer scans being ordered than the appropriate use criteria would allow. Although few in number, five of nine advanced dementia patients with MoCA <10 had an amyloid PET scan as part of their clinical workup, indicating that diagnostic uncertainty may remain even in late-stage disease and that in some cases clinicians thought amyloid PET scans in this group would positively impact care and management.

**TABLE 2** Clinical differences between patients with and without an amyloid PET scan as part of workup

| Clinical characteristics of patients | Patient with an amyloid PET scan *n*= 197 | Patients without an amyloid PET scan *n*= 368 | *p* |
|---|---|---|---|
| Age in years [a] (SEM) | 69.57 (±0.42) | 76.04 (±0.49) | <0.001* |
| Male gender, *n* (%) | 190 (96.4%) | 359 (97.6%) | 0.41 |
| Vascular risk factors, *n* (%) | | | |
| History of stroke | 25 (12.6%) | 45 (12.2%) | 0.90 |
| Hypertension | 129 (65.2%) | 271 (73.8%) | 0.03 |
| Diabetes | 56 (28.3%) | 109 (29.0%) | 0.86 |
| Coronary artery disease | 39 (19.7%) | 98 (26.7%) | 0.06 |
| Psychiatric comorbidity, *n* (%) | | | |
| History of PTSD | 72 (36.4%) | 98 (26.7%) | 0.02 |
| Depression | 74 (37.4%) | 114 (31.0%) | 0.44 |
| Substance abuse | 75 (37.9%) | 127 (34.6%) | 0.12 |
| Any psychiatric disorder or substance disorder present | 120 (60.9%) | 183 (50.0%) | 0.01 |
| Cognitive syndrome | *n* = 192 | *n* = 358 | <0.001* |
| Unimpaired | 0 (0%) | 10 (2.8%) | 0.02 |
| SCD | 4 (2.1%) | 28 (7.8%) | 0.01 |
| Mild cognitive impairment | 124 (64.6%) | 184 (51.4%) | <0.005 |
| Dementia | 64 (33.3%) | 136 (38.0%) | 0.28 |
| Suspected primary etiology | *n* =174 | *n* =261 | |
| | Prior to scan: | After initial evaluation: | |
| AD | 107 (61.5%) | 112 (42.9%) | <0.001* |
| Non-AD | 57 (32.8%) | 136 (52.1%) | |
| Unclear diagnosis | 10 (5.7%) | 13 (5.0%) | |
| Met Appropriate Use Criteria | 193/197 (98.0%) | 210/326 (64.4%) | <0.001* |
| MoCA score[a] (SEM) | 20.29 (±0.35) | 19.88 (±0.25) | 0.33 |
| *N* | *n* = 191 | n = 354 | |
| MMSE[a] (SEM) | 24.48 (±0.28) | 24.33 (±0.20) | 0.65 |
| *N* | *n* =195 | *n* =363 | |
| Cognitive Testing | | | |
| CERAD Encoding total[a] | 13.84 (±0.35) | 14.00 (±0.24) | 0.70 |
| Delayed recall[b] | 4 (IQR 1-5) | 3 (IQR 1-5) | 0.79 |
| Corrected Recognition[b] | 8 (IQR 7-10) | 8 (IQR 6-10) | 0.95 |
| Instances of rapid forgetting[b] | 0 (0-2) | 0 (0-2) | 0.67 |
| Presence of rapid forgetting | 93 (47.7%) | 166 (45.7%) | 0.65 |
| Trail Making Test A, time | 47 (IQR 37-71) | 54 (IQR 40-80) | 0.05 |
| Trail Making Test B, time | 114 (IQR 77-192) | 136 (IQR 90-216) | 0.049 |
| FAS[b] | 27 (IQR 21-35) | 27 (IQR 20-36) | 0.26 |
| Total Categories[b] | 29 (IQR 20-38) | 28 (IQR 21-35) | 0.60 |
| FAS/CAT[b] | 0.92 (IQR 0.72-1.25) | 0.98 (IQR 0.77-1.30) | 0.12 |
| Boston Naming Test[b] | 13 (IQR 12-14) | 13 (IQR 11-14) | 0.52 |
| Geriatric Depression Scale[b] | 4 (IQR 2-7) | 4 (IQR 2-7) | 0.92 |
| Geriatric Anxiety Inventory[b] | 4 (IQR 1-11) | 3.5 (IQR 1-10) | 0.52 |

(Continues)

**TABLE 2** (Continued)

| Clinical characteristics of patients | Patient with an amyloid PET scan *n*= 197 | Patients without an amyloid PET scan *n*= 368 | *p* |
|---|---|---|---|
| MRI | | | |
| Anterior temporal atrophy | 66 (33.3%) | 128 (34.9%) | 0.70 |
| Medial temporal atrophy | 108 (54.5%) | 186 (50.7%) | 0.39 |
| Parietal atrophy | 78 (39.4%) | 141 (38%) | 0.74 |
| Frontal atrophy | 52 (26%) | 97 (26%) | 1.00 |
| Presence small vessel disease | 86 (43.4%) | 175 (47.7%) | 0.32 |
| Lacunar strokes | 12 (6%) | 42 (11.4%) | 0.04 |
| Presence microhemorrhages | 7 (3.5%) | 33 (8.9%) | 0.02 |

Values represent number of patients (%), standard error of the mean (SEM), or medians with interquartile ranges (IQR). All percentages are column percentages rather than row percentages. MoCA= Montreal Cognitive Assessment; MMSE = Mini-Mental Status Examination;
[a]*t*-test.
[b]Mann-Whitney *U* test.
*Were significant after correcting for multiple comparisons using Bonferroni correction at adjusted cutoff of $p < 0.001$.

Few patients in the current study received either FDG-PET ($n$ = 16) or lumbar punctures ($n$ = 4). Therefore, clinicians often determine that there is additional clinical benefit, and/or reduced patient burden, associated with an amyloid PET scans rather than an FDG-PET scan or lumbar puncture procedure. Furthermore, in some cases, FDG-PET may provide complementary and additive information in combination with amyloid PET, as others have suggested.[20]

Others have previously examined the utility of the current appropriate use criteria in determining which patients will benefit in terms of increased diagnostic confidence and a change in their management plan in a European memory disorders clinic.[6] They reported that more patients may benefit from amyloid PET studies than would otherwise receive an amyloid PET based on the current appropriate use criteria.[6] Similar findings from other groups also reported changes in management resulting from amyloid PET scan ordering regardless of adherence to appropriate use criteria.[21,22] It is possible that for patients in whom amyloid PET scans were not ordered, regardless of their adherence to current appropriate use criteria, could have also benefited from a scan in terms of increased diagnostic confidence and change in management, although this cannot be commented on in the current study. The current study shows that specialty trained clinicians use clinical judgement in addition to the appropriate use criteria in determining when to order scans rather than indiscriminately implementing the appropriate use criteria and ordering scans using that algorithm alone.

Using the rate of patients who met appropriate use criteria in the entire cohort (whether or not they received a scan), we determined that 77% of memory clinic patients overall had a suspected AD diagnosis as part of the differential. This percentage is in line with those of the Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) study that reported AD as the suspected etiology among 73% of patients with MCI and 82% of patients with dementia prior to PET scan.[23] The percentage of positive amyloid PETs (36.5%) in the current study is less than that of prior studies, which were in the range of 49% to 64%.[24–27] Of note, the appropriate use criteria were developed in a non-veteran setting and have not been previously applied and reported in a medically complex group similar to that of the current study; therefore we believe that the rate of positivity in the current study is in line with the high rates of co-morbid vascular, psychiatric, and traumatic brain injury, all of which impact cognition among older veterans. Furthermore, there is putative value in ruling out as well as ruling in AD, and in a veteran population amyloid PET studies may have a particular value for ruling out AD.

Finally, it is worth noting that in the current study, the average age of participants who received an amyloid PET scan was 69 years , as compared to a median age of 75 years in the IDEAS study, which excluded participants younger than age 65. In clinical practice when scans are being used, as in the current study, there is a tendency to order scans more commonly in younger patients to avoid specificity concerns in older patients who have higher prevalence rates of amyloid positivity. Thus a younger population, as in the current study, may tend to have lower rates of amyloid PET positivity and this may partially explain the lower rates of amyloid PET positivity in the current study as compared to the IDEAS study in particular.

The recent FDA approval of aducanumab for AD—initially in all stages and then later in only the mild stage—was based on the clearance of amyloid beta from the brain of participants in clinical trials. Although it is not clear that amyloid removal results in cognitive rescue or disease modification, the reality is that patients will begin requesting treatment with aducanumab. Clinicians will need to counsel patients despite conflicting therapeutic evidence and, if appropriate, prescribe this drug while monitoring for side effects of edema and hemorrhage, which occurred in up to 40% of clinical trial participants.[28] Prior to prescription, the demonstration of amyloid pathology will become imperative in patients under consideration for this therapy to confirm that amyloid plaques are, indeed, present. This set of circumstances, in turn, raises a myriad of potential systems issues surrounding amyloid PET use in clinical practice including financing for a growing number of relatively costly amyloid PET studies not currently covered by insurance. Perhaps the appropriate use criteria will need to

be revised to include patients under consideration for aducanumab therapy.

Group level differences were found in patients who underwent an amyloid PET versus those who did not, in that those who underwent a PET scan were younger and were more likely to have a suspected diagnosis of AD at their initial visit (Table 2). Not surprisingly, we found that use of regression models that younger age at presentation and a suspected AD etiologic diagnosis at presentation were the most highly predictive features of amyloid PET scan ordering in our clinic.

Large prospective studies such as the Imaging Dementia-Evidence for Amyloid Scanning (or IDEAS)[23] and Amyloid Imaging to prevent Alzheimer's disease (AMYPAD)[29] studies were designed primarily to answer questions about clinical management and utility resulting from amyloid PET scan ordering. However, both studies are limited in their ability to report data regarding ordering practices, as amyloid PET scan ordering was constrained to a research setting in both trials, rather than available as part of clinical care as in the current study. Furthermore, clinical trials of amyloid PET use lack associated costs for medical systems, and therefore cannot address how clinicians make systems level determinations regarding utility in clinical practice of amyloid PET ordering. These studies contrast the current study where the PET scans have costs for the medical system (although not a cost to patients). Thus the current study design is best able to answer questions related to naturalistic ordering practices among clinicians operating within a health care system with associated ordering costs.

Although it is still unclear to what extent the current findings are generalizable outside the VA system, the current results have direct bearing on the VA, the largest US health care system. Furthermore, prior studies describing the prevalence of dementia among US veterans have reported similar prevalence of Alzheimer's disease compared to the general US population,[30] suggesting that there may be some degree of generalizability of the current findings regarding rates of amyloid PET ordering in a VA tertiary clinic to those of tertiary academic medical centers.

## 5 | LIMITATIONS

This study was conducted in an academic tertiary memory disorders clinic in a predominantly male, veteran population, which may not be generalizable to a community clinic and/or a non-veteran population. Determination of appropriate use criteria adherence using retrospective chart review may be limited by an inability to fully determine a clinician's degree of confidence in AD as an etiological diagnosis at the time of amyloid PET ordering and clinician documentation may always not fully explain reasoning for ordering amyloid PET in some cases.

## 6 | CONCLUSIONS

In summary, the current study has reported for the first time how often amyloid PET scans might be ordered in an academic tertiary care cognitive and behavioral neurology sub-specialty memory disorders clinic. We found the rate to be slightly more than one-third of patients seen, and that ordering practices largely adhered to appropriate use criteria. In addition, fewer patients than those technically eligible for an amyloid PET scan based on current appropriate use criteria had a scan ordered by clinicians, indicating that clinicians use clinical judgement when implementing appropriate use criteria for amyloid PET ordering.

## CONFLICTS OF INTEREST

Ana Vives-Rodriguez, Kylie Schiloski, Anna Marin, Ryan Wang, Patrick Hajos, Prabhjyot Singh, Rachel Powsner, Katherine Turk, and Renee Decaro have no conflicts of interest to report. Andrew Budson has been a consultant for Eli Lilly, Corium, Cognito, and Sage; a grant recipient from Cyclerion; and a clinical trial investigator for Biogen, Eli Lilly, vTv therapeutics, and Cognito. Andrew E. Budson was supported by a VA Merit Award (CX001698). Andrew E. Budson and Katherine W. Turk were investigators on National Institutes of Health/National Institute on Aging (NIH/NIA) P30 (AG072978). Katherine W. Turk was supported by a VA Career Development Award (CX002065). Author disclosures are available in the supporting information.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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