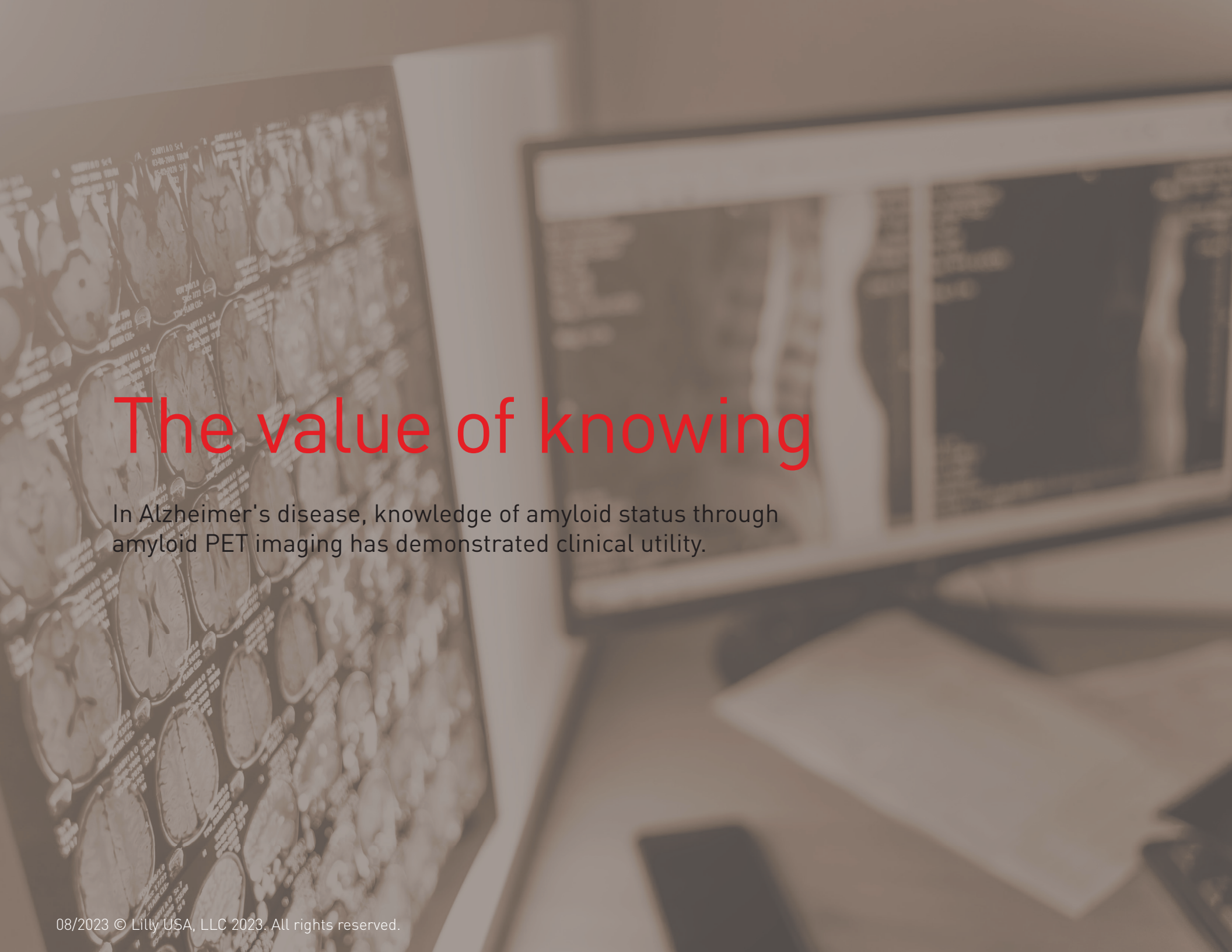


The value of knowing

In Alzheimer's disease, knowledge of amyloid status through amyloid PET imaging has demonstrated clinical utility.

Amyloid positron emission tomography, or PET, is a noninvasive diagnostic test used to aid in the diagnosis of adults with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive decline. The FDA recognized the clinical utility of amyloid PET with the approval of the first amyloid imaging agent in 2012, and this utility has been reinforced in numerous studies.

Currently, a 2013 Centers for Medicare & Medicaid Services (CMS) coverage decision restricting coverage of amyloid PET stands between patients with suspected AD and the diagnostic clarity that amyloid PET could provide. It is time for these restrictions to be lifted.

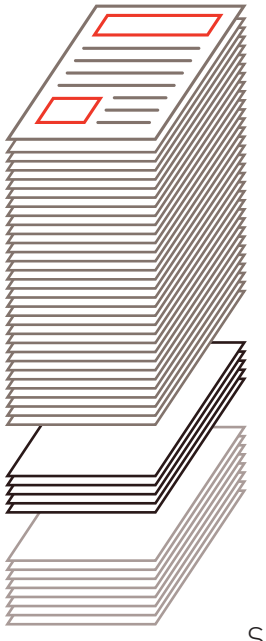
Table of Contents

Impressive evidence meets a growing need.

The evidence demonstrating the clinical utility of amyloid PET is extensive, persuasive, and covers a range of clinical scenarios.

And, the volume of evidence supporting the value of amyloid PET imaging in aiding the diagnosis of patients with suspected AD has culminated at a key moment, the arrival of targeted anti-amyloid therapies.

More than 40 studies in over 20,000 patients have evaluated or utilized amyloid PET



33 studied clinical utility, including long-term outcomes[1-33]

6 studied appropriate use criteria (AUC)[2,14,34-37]

11 studied drugs in development[38-48]

See study summaries in Body of Evidence, beginning on page 12.

Aβ PET has repeatedly and consistently demonstrated positive impact on patient care.

The clinical utility of amyloid PET

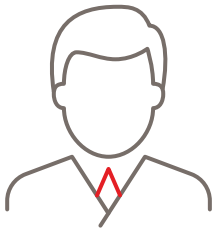
Amyloid PET imaging has substantial clinical utility, even in the absence of disease-modifying therapeutics. Results of multiple studies agree: in patients with dementia of unknown cause, amyloid PET frequently changed clinical management, changed patient diagnoses, and improved provider confidence in the patient's diagnosis. It can also help direct referrals to clinical trials, AD genetic testing, addition or removal of planned diagnostic tests, and counseling.[1-31]

Knowing amyloid status adds clarity to the management of patients with suspected AD

When amyloid PET allows providers and patients to know amyloid status, it allows them to shape better care plans. Importantly, this is true even of a negative scan. When amyloid PET indicates that the cause of cognitive decline is unlikely to be AD, providers and patients can avoid unnecessary treatments and look into other possible causes.[1-4,6,7,9,12,15,19,22,24-31]

Summary of studies evaluating amyloid PET clinical utility[49]

Change in diagnosis

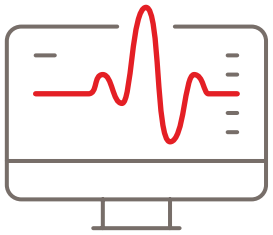


IN

~30%

OF PATIENTS

Gain in diagnostic confidence



IN

~60%

OF PATIENTS

Overall change in management

IN

~60%

OF PATIENTS

VA CONFIRMED

Independent research from the VA confirms amyloid PET's clinical utility.

The Department of Veterans Affairs (VA), one of the nation's leaders in independent health research, has conducted 2 studies that add significant weight to the assessment of amyloid PET's clinical value. The first was a study of 565 veterans treated in the Memory Disorders Clinic at VA Boston,[37] where neurologists could order amyloid PET scans at their discretion. It was found that patients and clinicians chose to do so in more than a third of cases, highlighting the scans' perceived utility.

In a follow-up study of the 197 patients who received an amyloid PET scan,[31] 53% had a change in diagnosis following amyloid PET imaging. Only 37% were amyloid positive, a lower-than-expected positivity rate demonstrating that, in these medically complex patients, the utility of amyloid PET imaging was largely found in ruling out AD. Meanwhile, a positive scan was associated with less follow-up in the clinic, fewer additional diagnostic tests, more prescriptions for AD medications, and more research referrals.

The VA researchers hope their studies will lead to greater use of amyloid PET scans in VA and potentially outside it as well, if the policies of insurance companies change.[50]

> "...[Our research on amyloid PET scans] just shows how useful they've been and that we've come to rely on them."
>
> —Dr. Katherine Turk, neurologist at VA Boston Healthcare System and co-author of the research[50]

Amyloid PET contributes to improved long-term outcomes.[46]

Recent research by van Maurik and colleagues evaluating the long-term health benefits of amyloid PET provides important contributions to the body of evidence supporting amyloid PET.

In this study of patients evaluated at a tertiary memory clinic as part of the ABIDE-PET project (see page 39 for a detailed description), amyloid PET imaging was offered to all patients as part of their diagnostic workup for AD. Patients who accepted were propensity score matched (which compensates for putative selection bias) with patients who did not undergo amyloid PET imaging. These matched groups (444 patients in each group) were then compared. The study provided solid evidence that adding amyloid PET imaging to the diagnostic workup contributed to better health outcomes later in the disease trajectory.

Lower risk of institutionalization

Amyloid PET	No Amyloid PET
10% (n=45)	**21%** (n=92)

Over a 3-year period
(HR: 0.48; 0.33-0.70)

Translates to a delay of 1.5 years in 5% institutionalization

Lower mortality

Amyloid PET	No Amyloid PET
11% (n=49)	**18%** (n=81)

Over a 4-year period
(HR: 0.51; 0.36-0.73)

Corresponds with a 1.4 year longer survival after diagnosis

Lower care costs

Amyloid PET vs No Amyloid PET

- Institutional costs (largest contributor)
- General practitioner costs
- Psychological costs
- Transportation costs

Over a 4-year period

Considering institutionalization is the driving force in dementia care, even a small delay could provide tremendous potential for cost savings

The range of clinical scenarios for amyloid PET is far broader than previously defined.

The 2013 CMS decision limited coverage of amyloid PET to narrowly defined and clinically difficult differential diagnoses, such as AD versus frontotemporal dementia, based on AUC published at that time.

Nearly a decade later, several catalogued studies certainly support this narrow usage, but several others have demonstrated much broader clinical utility, consistently finding evidence of value in both AUC and non-AUC patients.[2,14,34-37]

AUC limit amyloid PET to:

- Unexplained cognitive impairment, >65 years of age, with possible AD but unusual presentation
- Progressive young-onset dementia

Amyloid PET has played a role in clinical trials of amyloid-lowering therapies for AD.

In 2013, CMS recognized the promise of amyloid PET imaging for enriching clinical trials of potential AD therapeutics, by allowing for selection of patients on the basis of biological as well as clinical and epidemiological factors.[51]

Because patients without amyloid pathology are unlikely to benefit from amyloid-lowering therapy, use of amyloid PET has become an important part of identifying patients eligible for clinical trials of these agents.[38-48] This key requirement is based on learnings from early trials that enrolled patients using clinical criteria only, which has limited sensitivity and specificity for AD pathology. In fact, in one trial that did not require amyloid PET imaging for inclusion, approximately 25% of patients were later found to not have evidence of amyloid-related disease.[43]

Amyloid PET imaging has also been used as an outcome marker in multiple clinical drug-development trials, including those of amyloid-lowering therapies in late stage development. Data from these trials have shown that it can be effective for monitoring and assessing their ability to reduce, or clear, neuritic amyloid plaques.[38-48] The use of amyloid PET in these trials has contributed to understanding of AD, and provided learnings that may lead to more effective options. For example, experts suggest the recent failure of one of these agents as possibly related to its underwhelming impact on amyloid, an insight that would have not been possible without amyloid PET data.[52,53]

What's more, results of amyloid PET have been used to identify patients who have cleared amyloid and can then stop treatment.[41]

In trials for development of anti-amyloid therapies, amyloid PET has shown value in key areas[38-48]

Identifying patients for inclusion

Assessing response to treatment

In the case of one agent, informing treatment completion

Amyloid PET may support an earlier clinical diagnosis of patients with AD.[33]

As AD progresses, increasingly severe symptoms significantly burden patients and their caregivers. Diagnosis in early stages can provide patients the opportunity to collaborate in the development of advance care plans and seek early interventions that could help reduce cognitive, functional, and behavioral decline.[54]

The Amyloid Imaging to Prevent Alzheimer's Disease Diagnostic and Patient Management Study,* a prospective, multicenter, randomized clinical trial, investigated the use of amyloid PET early vs late in the diagnostic workup of 794 patients evaluated at a memory clinic for cognitive concerns considered to be possibly due to AD.

Amyloid PET performed early in the diagnostic workup allowed patients to receive an etiological diagnosis with very high confidence after only 3 months

Patients with very high diagnostic confidence after 3 months

40% Early PET†

11% Late PET†

3.5x more frequently

Patients who received amyloid PET early† in their diagnostic workup:

- **More** often had a change in diagnosis than patients who received it late† (44% vs 11%, respectively)
- **More** often were reclassified from AD to non-AD, always after a negative amyloid PET scan, than patients who received it late† (26% vs 5%, respectively)

> "A timely high-confidence diagnosis is critical to the efficacy of disease-modifying therapies, especially anti-amyloid drugs, whose efficacy might decrease with advancing disease progression."

*Patients from 8 European memory clinics (recruited April 16, 2018-October 30, 2020) were randomized to one of 3 study groups: arm 1, PET early in the diagnostic workup (within 1 month), arm 2, PET late in the diagnostic workup (after an average of 8 months), or arm 3, if and when the managing physician chose. The main outcome was the difference between arm 1 and arm 2 in the proportion of participants receiving an etiological diagnosis with very high confidence (≥90% on a 50%-100% visual numeric scale) after 3 months.

† "Early" was defined as within 1 month from baseline while "late" was defined as after a mean of 8 months from baseline.

SUMMARY

After a decade of accumulating evidence, broader coverage of amyloid PET imaging is warranted.

More than 40 studies in over 20,000 patients have evaluated amyloid PET imaging and consistently and conclusively demonstrated its clinical utility

With the availability of disease-modifying therapies, amyloid PET imaging must be broadly accessible to healthcare providers and patients considering treatment to help ensure timely identification of appropriate patients

References:

1. Rabinovici GD, et al. *JAMA*.2019;321:1286-94.
2. Apostolova LG, et al. *Alzheimers Dement (Amst)*. 2016;5:15-22.
3. Bensaïdane MR, et al. *J Alzheimers Dis.* 2016;52(4):1251-1262.
4. Boccardi M, et al. *JAMA Neurol*. 2016;73(12):1417-1424.
5. Brendel M, et al. *EurJ Nucl Med Mol Imaging*. 2017;44(13):2239-2248.
6. Carswell CJ, et al. *J Neurol Neurosurg Psychiatry*. 2018;89(3):294-299.
7. Ceccaldi M, et al. *Alzheimers Dement*. 2018;14(3):293-305.
8. Chételat G, et al. *Brain*. 2016;139(Pt 9):2528-2539.
9. de Wilde A, et al. *JAMA Neurol*. 2018;75(9):1062-1070.
10. Degerman Gunnarsson M, et al. *Dement Geriatr Cogn Dis Extra*. 2013;3(1):472-481.
11. Frederiksen KS, et al. *Dement Geriatr Cogn Dis Extra*. 2012;2(1):610-621.
12. Grundman M, et al. *Alzheimer Dis Assoc Disord*. 2013;27(1):4-15.
13. Hattori N, et al. *J Alzheimers Dis Rep*. 2020;4:165-174.
14. Hellwig S, et al. *EurJ Nucl Med Mol Imaging*. 2019;46(2):312-323.
15. Lage C, et al. *J Alzheimers Dis*. 2018;63(3):1025-1033.
16. Leuzy A, et al. *Eur J Nucl Med Mol Imaging*. 2019;46(6):1276-1286.
17. Mitsis EM, et al. *Mol Neurodegener*. 2014;9:10.
18. Ossenkoppele R, et al. *Alzheimers Dement*. 2013;9(4):414-421.
19. Pontecorvo MJ, et al. *Dement Geriatr Cogn Disord*. 2017;44(3-4):129-143.
20. Ramusino MC, et al. *EurJ Nucl Med Mol Imaging*. 2020;47(2):270-280.
21. Sánchez-Juan P, et al. *Neurology*. 2014;82(3):230-238.
22. Schipke CG, et al. Published correction appears in *Dement Geriatr Cogn Disord*.2012;34(3-4):262]. *Dement Geriatr Cogn Disord*. 2012;33(6):416-422.
23. Schönecker S, et al. *Nervenarzt*. 2017;88(2):156-161.
24. Shea YF, et al. *J Alzheimers Dis*. 2018;66:1599-1608.
25. Spallazzi M, et al. *J Alzheimers Dis*. 2019;67(4):1235-1244.
26. Triviño-Ibáñez EM, et al. *Medicine (Baltimore)*. 2019;98(29).
27. Weidman DA, et al. *Neurocase*. 2017;23(1):41-51.
28. Weston PS, et al. *J Alzheimers Dis*.2016;54(4):1297-1302.
29. Zannas AS, et al. *Neurocase*. 2014;20(4):466-473.
30. Zwan MD, et al. *Alzheimers Dement*.10: 2014;14.
31. Vives-Rodriguez A, et al. *Alzheimers Dement*. 2022;8:e12320.
32. van Maurik I, et al. *Alzheimers Dement*. 2022;1-8.
33. Altomare D, et al. *JAMA Neurol.* 2023;80(6):548-557.
34. Altomare D, et al. *Alzheimers Dement*. 2018;14:1088-1098.
35. De Wilde A, et al. *Alzheimers Dement*. 2019; https://doi.org/10.1016/j.jalz.2019.07.003.
36. Grundman M, et al. *Dement Geriatr Cogn Disord*. 2016;41:80-92.
37. Turk KW, et al. *Alzheimers Dement*. 2022;8:e12333.
38. Brody M, et al. *J Alzheimers Dis*. 2016;54(4):1509-1519.
39. Salloway S, et al. *Alzheimers Res Ther*. 2018;10(1): 96.
40. Lowe SL, et al. *J Prev Alzheimers Dis*. 2021;8(4):414-424.
41. Mintun MA, et al. *N Engl J Med*. 2021;384(18):1691-704.
42. Fleisher AS, et al. *Alzheimers Dement*. 2017;13(10):1117-1124.
43. Honig LS, et al. *N Engl J Med*. 2018;378(4):321-330.
44. Michelson D, et al. *J Prev Alzheimers Dis*. 2019;6(4):228-231.
45. Cummings JL, et al. *Alzheimers Res Ther*. 2016;8:4.
46. van Dyck CH, et al. *N Engl J Med*. 2022; doi:10.1056/NEJMoa2212948
47. Safety and efficacy study of gantenerumab in participants with early Alzheimer's disease. Accessed December 6, 2022. https://clinicaltrials.gov/ct2/show/record/NCT03443973
48. Safety and efficacy study of gantenerumab in participants with early Alzheimer's disease. Accessed December 6, 2022. https://clinicaltrials.gov/ct2/show/record/NCT03444870
49. Barthel H, Sabri O. *J Nucl Med*. 2017;58:1711-1717.
50. US Department of Veterans Affairs. VA-led research finds PET scans important for ruling out Alzheimer's disease. Accessed September 29, 2022. https://www.research.va.gov/currents/0922-VA-led-research-finds-PET-scans-important-for-ruling-out-Alzheimers-disease.cfm
51. CMS.gov. Beta amyloid amyloid positron tomography in dementia and neurodegenerative diseases. Accessed September 9, 2022. https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=356&ncdver=1
52. Alzheimer's Association statement on gantenerumab phase 3 topline data release. Accessed December 9, 2022. https://www.alz.org/news/2022/statement-gantenerumab-phase-three-results
53. Gantenerumab falls short in phase 3. Accessed December 9, 2022. https://www.alzforum.org/news/research-news/gantenerumab-falls-short-phase-3-0
54. Porsteinsson AP, et al. *J Prev Alz Dis.* 2021;3(8):371-386.

Body of Evidence

- Clinical Utility Studies
- AUC Studies
- Drug Development Studies

Association of amyloid positron emission tomography with subsequent change in clinical management among Medicare beneficiaries with mild cognitive impairment or dementia

Rabinovici GD, Gatsonis C, Apgar C, et al. *JAMA*. 2019;32:1286-1294.

CONCLUSION

The use of amyloid PET imaging was associated with changes in clinical management within 90 days in the majority of patients, most commonly the use of AD drugs.

Purpose: To assess whether amyloid positron emission tomography (PET) imaging positively impacts diagnosis and management of cognitively impaired patients

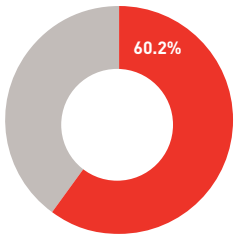
Methods

- 946 US dementia specialists registered 16,008 Medicare participants with mild cognitive impairment (MCI) or dementia of uncertain etiology
- Patients underwent a comprehensive diagnostic assessment (cognitive testing, laboratory testing, and head computed tomography or magnetic resonance imaging)
- A pre-PET diagnosis and management plan was documented prior to patients undergoing amyloid PET imaging
- Within 90 (±30) days after the amyloid PET scan, the diagnosis and management plan was again documented
- The primary endpoint was change between pre-PET and 90-day post-PET patient management in 1 or more of the following: Alzheimer's disease (AD) drug therapy, other drug therapy, or counseling about safety and future planning
- The secondary endpoint was the proportion of patients who changes in diagnosis (from AD to non-AD and vice versa) between pre- and post-PET visits

Key Results: Impact of amyloid PET imaging

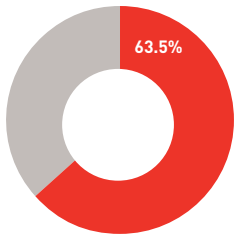
Amyloid PET imaging results frequently resulted in treatment plan changes

PATIENTS WITH MCI (n=6905)



Patients with a change in management post amyloid PET

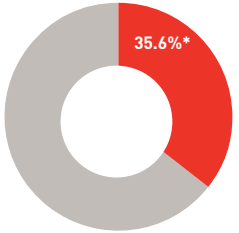
PATIENTS WITH DEMENTIA (n=4504)



Patients with a change in management post amyloid PET

Amyloid PET imaging resulted in a change in diagnosis in more than a third of patients

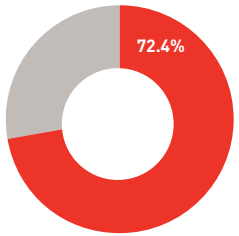
ALL PATIENTS (n=11,409)



Patients with a changed diagnosis post amyloid PET

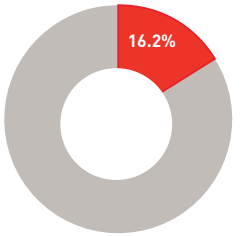
Amyloid PET imaging improved diagnostic confidence that AD pathology was contributing to cognitive impairment

PRE-PET (n=11,409)



Patients with uncertain diagnosis†

POST-PET (n=11,409)



Patients with uncertain diagnosis†

*The etiologic diagnosis changed from AD to non-AD in 2860 of 11,409 patients (25.1%) and from non-AD to AD in 1201 of 11,409 patients (10.5%), for a total of 35.6% of patients.
†4-7 on Likert scale ranging from 1 (definitely not) to 10 (certain).

Critical review of the appropriate use criteria for amyloid imaging: effect on diagnosis and patient care

Apostolova LG, Haider JM, Goukasian N, et al. *Alzheimers Dement*. 2016;5:15-22.

CONCLUSION

Amyloid imaging information frequently resulted in both diagnostic and treatment plan changes.

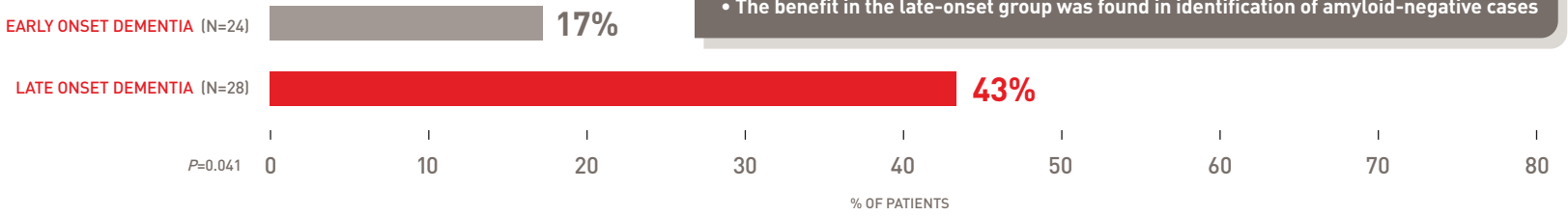
Purpose: To examine the utility of the Appropriate Use Criteria (AUC)* for amyloid imaging in evaluation of cognitive impairment

Methods

- 53 patients with cognitive impairment who received amyloid PET imaging for diagnostic purposes at a US tertiary medical center were classified as early onset (cognitive decline began before 65 years of age) or late onset (cognitive decline began after 65 years of age), as well as AUC-consistent or AUC-inconsistent*

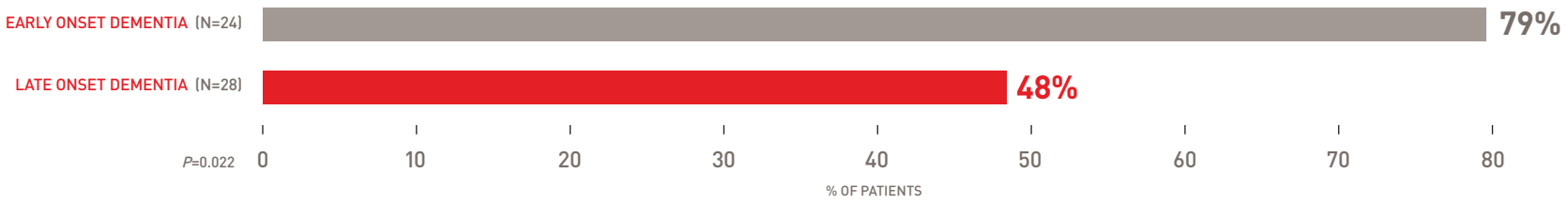
Key Results: Impact of amyloid PET imaging

Change in diagnosis was more common in late onset cognitive impairment than early onset



- The benefit in the early-onset group was found in confirmation of amyloid positivity and a diagnosis of AD, which is what prompted referral for the amyloid PET scan
- The benefit in the late-onset group was found in identification of amyloid-negative cases

Changes in treatment were more common in early onset cognitive impairment than late onset



*AUC includes patients with progressive mild cognitive impairment 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.

Clinical utility of amyloid PET imaging in the differential diagnosis of atypical dementias and its impact on caregivers

Bensaidane MR, Beauregard JM, Poulin S, et al. *J Alzheimers Dis.* 2016;52:1251-1262.

CONCLUSION

In atypical cases of dementia with an unclear diagnosis, amyloid PET imaging increased diagnostic confidence, led to significant alterations in management, and had a positive impact on caregivers' lives.

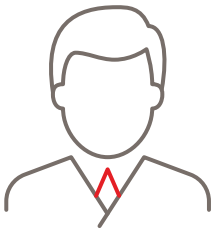
Purpose: To investigate the clinical utility of amyloid positron emission tomography (PET) imaging in the differential diagnosis of early-onset atypical cases of dementia

Methods

- 28 patients ≤65 years old who had an atypical/unclear dementia diagnosis despite a comprehensive evaluation (history, detailed neurological examination, blood tests, comprehensive neuropsychological evaluation, magnetic resonance imaging, and 18F-fluorodeoxyglucose-PET) underwent amyloid PET imaging
- Physicians were asked to evaluate whether the amyloid PET results led to a change in diagnosis or altered management and reported their degree of confidence in the diagnosis (scan of 1 to 5 where 1=very weak, 2=weak, 3=average, 4=high, and 5=very high)
- Caregivers completed a questionnaire/interview to assess the impact of the amyloid PET scan results on anxiety, depression, disease perception, future anticipation, and quality of life

Key Results: Impact of amyloid PET imaging (N=28)

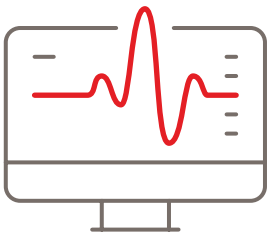
Change in diagnosis



32.1%

OF PATIENTS

Improved diagnostic confidence



44%

INCREASE IN DIAGNOSTIC CONFIDENCE

Changes in management

71.4%

OF PATIENTS

- All patients who were amyloid positive and had a change in diagnosis also had a change in medication (initiation or modification of Alzheimer's disease medication)
- Patients who were amyloid negative but were previously on Alzheimer's disease medication had it discontinued
- Besides medication changes, changes in management may have included clinical trial registration, additional tests, or referrals

Positive impact on caregivers' lives

- Of the 23 caregivers met, knowledge of the patient's amyloid status improved anxiety, depression, disease perception, future anticipation, and quality of life

Assessment of the incremental diagnostic value of florbetapir F 18 imaging in patients with cognitive impairment: the incremental diagnostic value of amyloid PET with ^{18}F-florbetapir (INDIA-FBP) Study

Boccardi M, Altomare D, Ferrari C, et al. *JAMA Neurol*. 2016;73:1417-1424.

CONCLUSION

Amyloid PET in addition to routine assessment in patients with cognitive impairment had a significant effect on diagnosis, diagnostic confidence, and drug treatment.

Purpose: To evaluate the value of amyloid PET with florbetapir F 18 in addition to the routine diagnostic assessment of patients evaluated for cognitive impairment

Methods

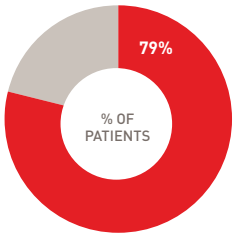
- In an open-label, multicenter study 228 patients with cognitive impairment were evaluated for AD and other causes of cognitive decline
- Dementia experts (neurologist or geriatrician) made a preliminary diagnosis based on cognitive, physical, and neurological examination prior to an amyloid PET scan and rated their confidence that cognitive impairment was due to AD, and prescribed drug treatment based on the pre-scan assessment
- After the amyloid PET scan was completed, dementia experts were asked to revise the patients' diagnosis, diagnostic confidence, and drug treatment

Key Results: Impact of amyloid PET imaging

Amyloid PET imaging resulted in a change in diagnosis for the majority of patients

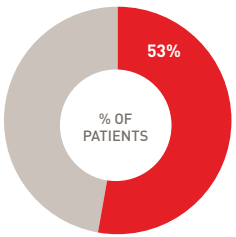
Among patients who had a previous AD diagnosis, but received a negative amyloid PET scan

CHANGE IN DIAGNOSIS



Among patients who had a previous non-AD diagnosis, but received a positive amyloid PET scan

CHANGE IN DIAGNOSIS



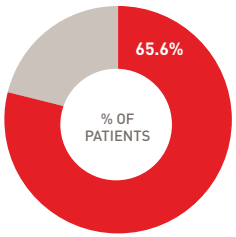
Amyloid PET imaging positively affected diagnostic confidence both after positive and negative scan results and for AD and non-AD diagnoses

DIAGNOSTIC CONFIDENCE

Amyloid PET results impacted treatment for both amyloid-positive and negative patients

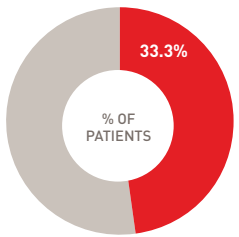
Introduction of cognition-specific medication in amyloid-positive patients

CHANGE IN MANAGEMENT



Discontinuation of cognition-specific medication in amyloid-negative patients

CHANGE IN MANAGEMENT



Additive value of amyloid-PET in routine cases of clinical dementia workup after FDG-PET

Brendel M, Schnabel J, Schonecker S, et al. *Eur J Nucl Med Mol Imaging*. 2017;44:2239-2248.

CONCLUSION

Amyloid PET imaging was highly valuable in establishing a final diagnosis in patients with cognitive impairment when prior tests were inconclusive. It was particularly beneficial in distinguishing AD from FTLD and is predicted to have a considerable impact on patient management, especially in light of potential availability of disease-modifying therapies.

Purpose: To assess the value of adding amyloid positron emission tomography (PET) in the diagnosis of patients with cognitive impairment when a battery of prior multi-modal assessments, including (^{18}F)-fluordeoxyglucose (FDG)-PET examinations, were insufficient to establish a diagnosis

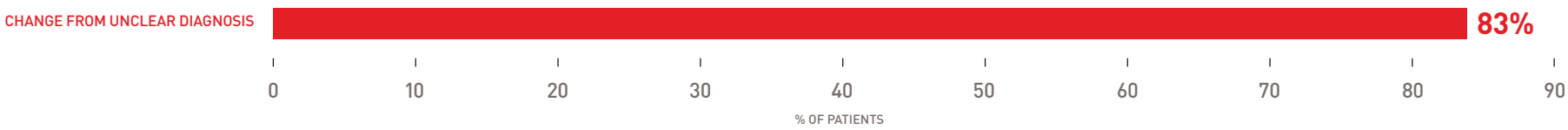
Methods

- 107 patients with mild cognitive impairment or dementia were recommended for amyloid PET imaging because their diagnosis was unclear after other evaluation methods (cognitive testing, magnetic resonance imaging, cerebrospinal fluid sampling, and FDG-PET examinations)
- Dementia experts recorded the most likely diagnosis before and after amyloid PET imaging was completed

Key Results: Impact of amyloid PET imaging (N=107)

The initial diagnosis was changed

A final diagnosis was determined



- **A negative amyloid PET scan was associated with a higher rate of diagnosis change (38%) than a positive scan (22%)**
- **The highest impact of amyloid PET imaging was in distinguishing Alzheimer's disease (AD) from fronto-temporal dementia (FTLD), where it altered the most likely diagnosis in 41% of patients**

*Information was missing for 3 patients.

Clinical utility of amyloid PET imaging with ^{18}F-florbetapir: a retrospective study of 100 patients

Carswell C, Win Z, Muckle K, et al. *Neurol Neurosurg Psychiatry.* 2018;89:294-299.

CONCLUSION

Amyloid PET imaging had a clear role in the work up of "real-world" patients with cognitive impairment by significantly affecting clinical management and improving diagnostic certainty.

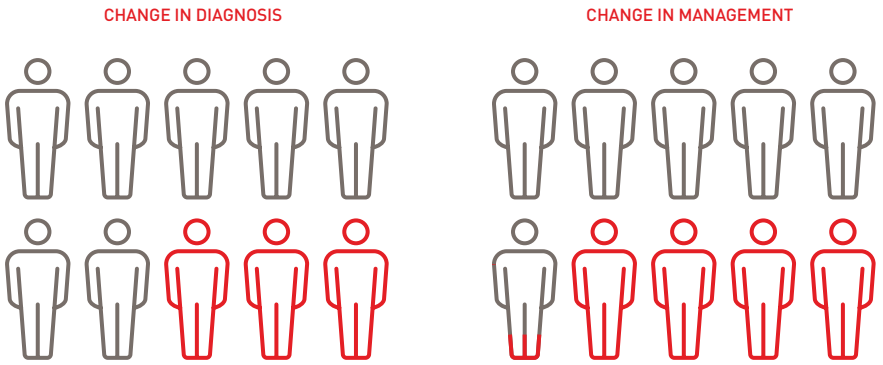
Purpose: To evaluate the clinical utility of including amyloid positron emission tomography (PET) as part of a diagnostic workup in "real-world" patients with cognitive impairment

Methods

- The presenting clinical features and cognitive investigations, diagnosis, and outcomes pre- and post-amyloid PET were evaluated in the first 100 patients undergoing amyloid PET imaging at a tertiary memory clinic

Key Results: Impact of amyloid PET imaging (N=100)

Amyloid PET was used primarily to investigate patients with atypical clinical features (56 patients) or those that were young at onset (42 patients)



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

Ceccaldi M, Jonveaux T, Verger A. *Alzheimers Dement.* 2018;14:293-305.

CONCLUSION

Amyloid PET imaging had a substantial impact on diagnosis and management of complex patients with uncertain AD diagnosis.

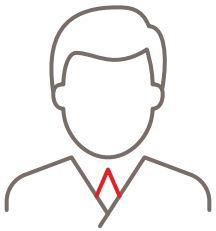
Purpose: To investigate whether amyloid PET imaging in patients undergoing investigation for AD leads to changes in diagnosis, diagnostic confidence, or alterations in management

Methods

- Multicenter, open-label study of 205 patients with complex situations (ie, early-onset, atypical clinical profiles, suspected mixed etiological conditions, unexpected rate of progression) for whom standard clinical assessment for Alzheimer's disease (AD) was not possible or inconclusive
- Each patient had 3 outpatient clinic visits: 1) a baseline visit to establish an initial diagnosis; 2) a visit where an amyloid PET scan was performed; and 3) a follow-up visit at which patients were informed of the PET scan result and a final diagnosis was made

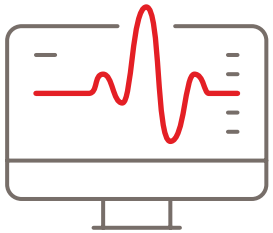
Key Results: Impact of amyloid PET imaging (N =205)

Change in diagnosis



66.8%
OF PATIENTS

Improved diagnostic confidence



81.5%
OF PATIENTS

Changes in management

80%
OF PATIENTS

- **50.7% of patients had a substantial change (ie, change in medication, additional diagnostic tests, or referral to a new specialist)**

Atrophy, hypometabolism, and clinical trajectories in patients with amyloid-negative Alzheimer's disease

Chetelat G, Ossenkoppele R, Villemagne VL, et al. *Brain*. 2016;139:2528-2539.

CONCLUSION

Amyloid PET imaging was useful in ruling out AD, particularly in patients without typical symptoms of AD.

Purpose: To evaluate characteristics of patients clinically diagnosed with Alzheimer's disease (AD) but who were subsequently amyloid negative on amyloid positron emission tomography (PET) imaging

Methods

- The characteristics of 40 patients who had a pre-amyloid PET diagnosis of probable AD (without taking into consideration imaging data) and subsequently found to be amyloid negative were evaluated

Key Results: Impact of amyloid PET imaging (N=37)*

Pet imaging resulted in a change in diagnosis in the majority of patients

- **48% of patients who predominantly had memory deficits typical of AD, but were amyloid negative, had a change in diagnosis**
- **94% of patients who did not have symptoms typical of AD had a change in diagnosis**

*Information was missing for 3 patients.

Association of amyloid positron emission tomography with changes in diagnosis and patient treatment in an unselected memory clinic cohort

De Wilde A, van der Flier W, Pelkmans W, et al. *JAMA Neurol*. 2018;75:1062-1070.

CONCLUSION

Both amyloid-positive and amyloid negative PET results were associated with important changes in diagnosis and treatment for patients with and without dementia.

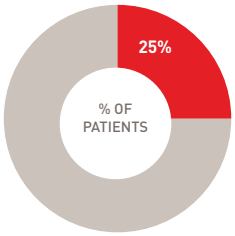
Purpose: To evaluate the association between use of amyloid positron emission tomography (PET) in patients being evaluated for cognitive impairment and changes in diagnosis, diagnostic confidence, and treatment

Methods

- Amyloid PET imaging was offered to patients with dementia, mild cognitive impairment, or subjective cognitive decline visiting a memory clinic for a diagnostic workup
- Prior to amyloid PET results being disclosed, neurologists established an initial diagnosis, level of diagnostic confidence (0% to 100%), and treatment plan (other investigations, initiation/withdrawal of Alzheimer's disease (AD) medications, initiation/withdrawal of care)
- After amyloid PET results were disclosed to the neurologists, they were asked to re-evaluate the patient's diagnosis and treatment

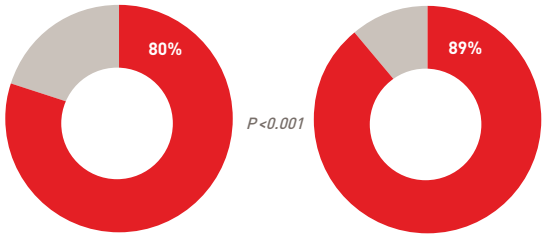
Key Results: Impact of amyloid PET imaging (N=507)

Change in diagnosis

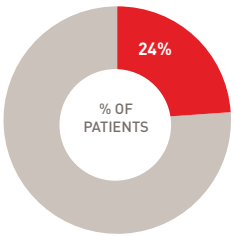


- Diagnosis changed more often because of a negative amyloid PET scan (31%) than a positive scan (18%)

Improved diagnostic confidence



Change in management



- The patient's treatment plan altered more often for patients with a positive amyloid PET scan (33%) than for those with a negative scan (16%) and consisted mainly of medication changes, clinical trial referral, or both
- After a negative amyloid PET scan, neurologists primarily performed additional investigations, genetic screening, referral to a psychiatrist, multiple investigations, or other

Re-evaluation of clinical dementia diagnoses with Pittsburgh compound B positron emission tomography

Gunnarson MD, Lindau M, Santillo AF, et al. *Dement Geriatr Cogn Disord Extra*. 2013;3:472–481.

CONCLUSION

The subtle differences between AD and non-AD dementia, and overlap of many features, highlight the need for amyloid biomarkers.

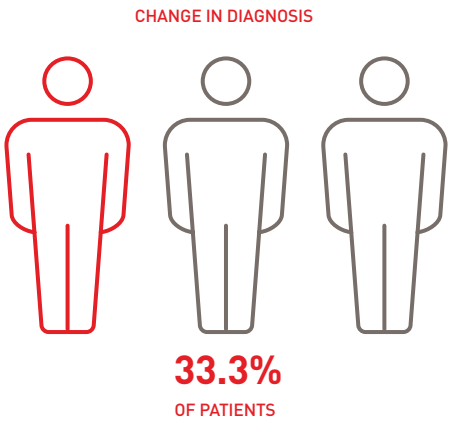
Purpose: To investigate whether there are any differences between amyloid-positive and amyloid-negative patients in a mixed cohort of patients with mild dementia regarding neuropsychological test performance and regional cerebral glucose metabolism

Methods

- 18 patients clinically diagnosed as probable Alzheimer's disease (AD) or frontotemporal dementia were examined with amyloid PET imaging, ^{18}F-fluoro-2-deoxy-D-glucose (FDG) PET imaging (to evaluate regional cerebral glucose metabolism), and neuropsychological tests, and followed for 5-9 years (or to death)

Key Results: (N=18)

Change in diagnosis: 1/3 of patients (6 out of 18)



Amyloid-positive patients had slower psychometer speed and more impaired visual episodic memory than amyloid-negative patients, otherwise performance did not differ between the groups

Added diagnostic value of ^{11}C-PiB-PET in memory clinic patients with uncertain diagnosis

Frederiksen KS, Hasselbalch SG, Hejl Am, et al. *Dement Geriatr Cogn Disord Extra.* 2012;2:610-621.

CONCLUSION

Amyloid PET imaging adds value to the specialist clinical evaluation and other supplemental diagnostic testing in patients with suspected AD.

Purpose: To evaluate the value of adding amyloid positron emission tomography (PET) to specialist clinical evaluation and diagnostic testing such as magnetic resonance imaging (MRI) and computed tomography (CT) in patients with uncertain diagnosis

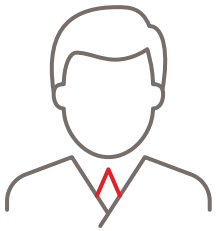
Methods

- Uncontrolled, retrospective study of 57 patients at a specialized neurology clinic who underwent amyloid PET imaging (^{11}C-PiB-PET) to confirm or rule out Alzheimer's disease (AD)
- Patients underwent a standard dementia evaluation including physical and neurological examination, cognitive and functional assessment, laboratory tests, structural scans (MRI and/or CT), functional imaging, and cerebrospinal fluid sampling
- Three experienced clinicians reached a consensus diagnosis and rated their confidence in the diagnosis before and after disclosure of amyloid PET results

Key Results: Even with extensive testing by dementia experts, adding amyloid PET imaging contributed to the diagnostic evaluation

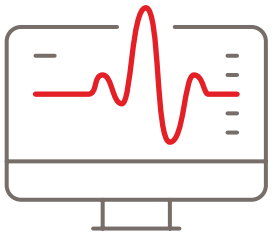
Impact of amyloid PET imaging on diagnosis and diagnostic confidence in patients with uncertain AD diagnosis (N=57)

CHANGE IN CONSENSUS DIAGNOSIS



23%
OF PATIENTS

IMPROVED DIAGNOSTIC CONFIDENCE



49%
OF PATIENTS

Potential impact of amyloid imaging on diagnosis and intended management in patients with progressive cognitive decline

Grundman M, Pontecorvo MJ, Salloway SP, et al. *Alzheimers Dis Assoc Disord.* 2013;27:4-15.

CONCLUSION

Amyloid PET imaging altered physician's diagnostic thinking, intended testing, and management of patients undergoing evaluation for cognitive decline.

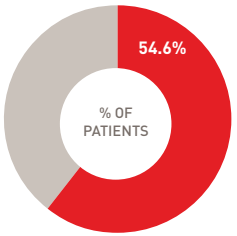
Purpose: To determine whether amyloid positron emission tomography (PET) imaging would alter a physician's diagnostic thinking and intended management in patients undergoing evaluation for cognitive decline

Methods

- 229 patients with a history of cognitive decline and uncertain diagnosis were evaluated (without the use of amyloid PET imaging) for the underlying cause of the decline
- Based on this evaluation, physicians recorded a diagnosis, along with their certainty/confidence (0% to 100%) in the diagnosis, a diagnostic testing plan, and a management plan
- Patients then underwent amyloid PET imaging using florbetapir F18 and the physician recorded a revised diagnosis and proposed treatment plan based on the results of the scan

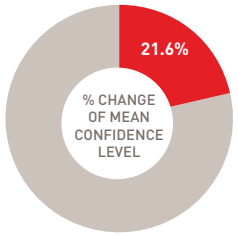
Key Results: Impact of amyloid PET imaging

Change in diagnosis (N=229)



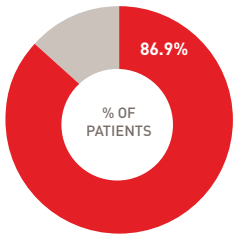
- 95% confidence interval: 48.1%-60.9%

Improved diagnostic confidence in patients who had an etiologic diagnosis before and after amyloid PET imaging (n=84)



- 95% confidence interval: 18.3%-24.8%

Change in management (N=229)



- Amyloid PET imaging particularly affected intended medication management
- In 31% of patients, results led to an intended change in Alzheimer's disease (AD) medications
- In 16.2% of patients, results led to a change in planned referral for participation in a clinical trial
- In 7.4% of patients, results led to an intended change in treatment with psychiatric medications (antidepressants, antianxiety medications, or antipsychotics
- In patients with a negative scan, planned use of AD medications was reduced by 23.3% (49.1% before the scan to 25.9% after the scan)

Reduced planned use of other testing modalities in patients whose workup was in progress (n=119)

-28.9%	LABORATORY TEST
-24.4%	BRAIN STRUCTURAL IMAGING
-32.8%	NEUROPSYCHOLOGICAL TESTING
-94.7%	LUMBAR PUNCTURE FLUORODEOXY
-91.3%	GLUCOSE PET
-50.0%	ApoE GENOTYPING

Initial physician experience with (^{18}F) flutemetamol amyloid PET imaging following availability for routine clinical use in Japan

Hattori N, Sherwin P, Farrar G. *J Alzheimers Dis Rep*. 2020;4:165-174.

CONCLUSION

Amyloid PET imaging led to a change in diagnosis in over 30% of cases and to a ~20% increase in diagnostic confidence.

Purpose: To assess the association of amyloid PET imaging and changes in diagnosis and diagnostic confidence

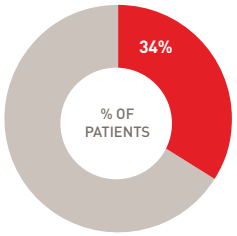
Methods

- As part of a Japanese post-approval study, 44 patients, who were being evaluated in clinical practice, underwent amyloid PET imaging with (^{18}F) flutemetamol because the referring physician believed the result would add value to the diagnostic workup/clinical assessment

Key Results:

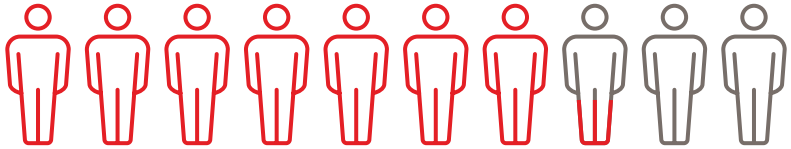
Amyloid PET imaging led to a change in diagnosis for ~1/3 of patients

CHANGE IN DIAGNOSIS (N=44)

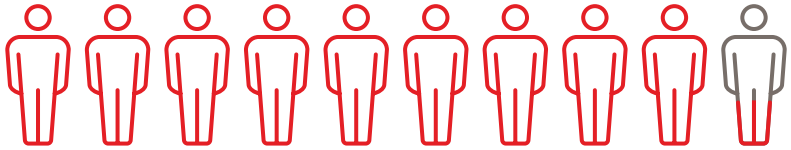


Amyloid PET imaging increased diagnostic confidence by ~20%

PRE-SCAN CONFIDENCE (N=44)



POST-SCAN CONFIDENCE (N=44)



Amyloid imaging for differential diagnosis of dementia: incremental value compared to clinical diagnosis and (^{18}F) FDG PET

Hellwig S, Frings L, Bormann T, et al. *Eur J Nucl Med Mol Imaging.* 2019;46:312-323.

CONCLUSION

Amyloid PET imaging provided significant incremental diagnostic value beyond clinical and [^{18}F] FDG PET diagnosis of AD.

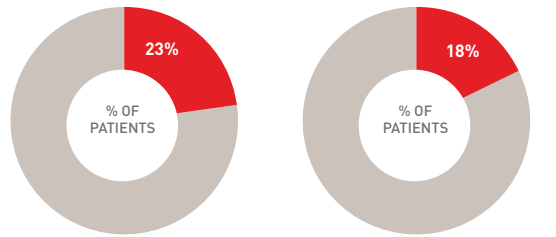
Purpose: To evaluate the incremental diagnostic value of amyloid positron emission tomography (PET) in addition to clinical diagnosis and (^{18}F) FDG PET in a real-life memory clinic population

Methods

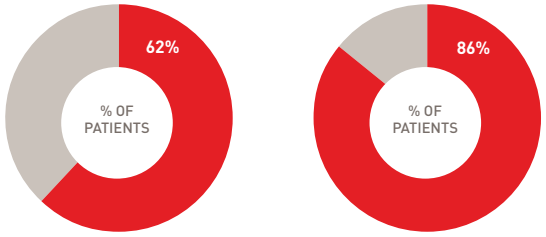
- 138 patients with cognitive impairment of uncertain etiology (complicated presentation) were referred for diagnostic imaging with amyloid PET imaging and [^{18}F] FDG PET
- Dementia experts determined a baseline diagnosis based on comprehensive clinical assessment and (^{18}F) FDG PET results, but not considering amyloid PET imaging results
- Of the 138 patients, 84 were diagnosed with neurocognitive disorders and were assigned to the following subgroups: 1) Alzheimer's disease (AD); 2) dementia with Lewy bodies (DLB); 3) fontotemporal dementia (FTD); or 4) non-neurodegenerative (NND) causes of major neurocognitive disorder (ie, alcohol-related dementia, vascular dementia, normal pressure hydrocephalus, psychiatric disorders)
- Results of amyloid PET imaging was disclosed to the dementia experts and they were asked to adjust their former diagnoses as necessary

Key Results: Impact of amyloid PET imaging (N=84)

Change in diagnosis

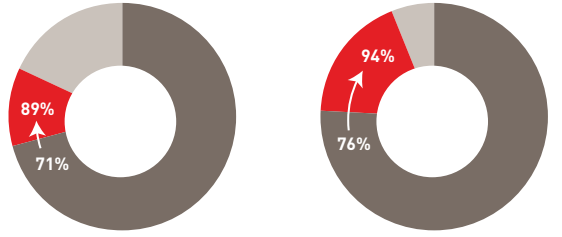


Improved agreement between clinical and (^{18}F) FDG PET diagnoses



- 24% increase in agreement (P<0.001)

Improved accuracy of clinical and (^{18}F) FDG PET diagnoses



- Clinical diagnosis improved from 71% to 89% (p<0.01)
- [^{18}F]FDG PET diagnosis improved from 76% to 94% (p<0.001)

Utility of amyloid and FDG-PET in clinical practice: differences between secondary and tertiary care memory units

Lage C, Suarez AG, Pozueta A, et al. *J Alzheimer's Dis.* 2018;63:1025-1033.

CONCLUSION

PET imaging commonly resulted in alterations in diagnoses and treatment among patients with cognitive impairment evaluated at a secondary memory clinic. Patients with MCI were significantly more likely to change diagnosis after PET imaging.

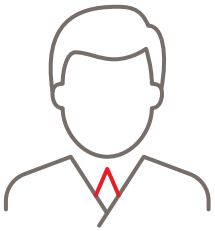
Purpose: To evaluate the effect of amyloid positron emission tomography (PET) imaging and fluorodeoxyglucose (FDG) PET imaging in clinical practice among patients with cognitive impairment referred by general practitioners

Methods

- Retrospective analysis of 151 patients who underwent FDG-PET and amyloid PET imaging at a secondary memory care unit
- Patients were assessed clinically by a neurologist before and after the scan
- FDG-PET and amyloid PET imaging results were revealed to the neurologist and changes between the pre- and post-PET clinical diagnosis and Alzheimer's disease (AD) treatment plan were reviewed

Key Results: Impact of amyloid PET imaging (N=151)

Change in diagnosis

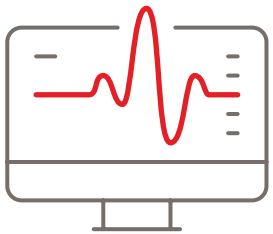


17.2%

OF PATIENTS

- Approximately 1/3 of all diagnostic changes took place in patients with mild cognitive impairment

Improved diagnostic confidence

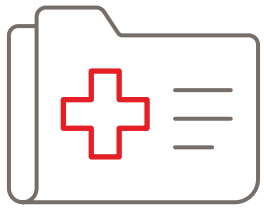


37.7% PRE-PET DIAGNOSTIC DILEMMAS

P=0.00002

15.6% POST-PET DIAGNOSTIC DILEMMAS

Change in treatment plan



45%

OF PATIENTS

- The most common change was the addition of an AD drug (85.3%)

Clinical impact of (^{18}F) flutemetamol PET among memory clinic patients with an unclear diagnosis

Leuzy A, Savitcheva I, Chiotis K, et al. *Eur J Nucl Med Mol Imaging.* 2019;46:1276-1286.

CONCLUSION

Amyloid PET imaging provided clinical value in terms of its impact on diagnosis, management and drug treatment, when added to the work-up of patients with an uncertain diagnosis in a tertiary memory clinic.

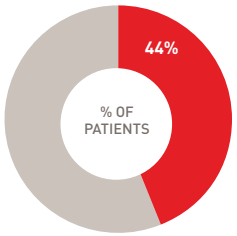
Purpose: To evaluate the effect of amyloid positron emission tomography (PET) imaging on changes in diagnosis and treatment in patients who had an unclear diagnosis following clinical assessment at a tertiary memory clinic

Methods

- 207 patients who had been referred for evaluation of cognitive impairment underwent a comprehensive assessment including neurological, psychiatric, and cognitive testing, computed tomography/magnetic resonance imaging, and cerebrospinal fluid sampling
- Amyloid PET imaging with (^{18}F) flutemetamol was performed and changes in diagnosis and the management plan were made based on the results when appropriate

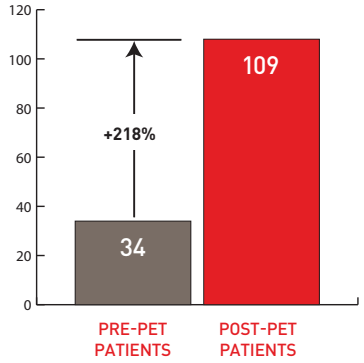
Key Results: Impact of amyloid PET imaging (N=207)

Change in diagnosis



- **A high percentage of patients (51%) with mild cognitive impairment had a change in diagnosis**
- **Those with dementia not otherwise specified also commonly had a change in diagnosis (55%)**
- **A change in diagnosis was less common among those with non-Alzheimer's disease (AD, 30%) and those with AD (20%)**

Increased use of AD medication (cholinesterase inhibitor)



A consecutive case series experience with (^{18}F) florbetapir PET imaging in an urban dementia center: impact on quality of life, decision making, and disposition

Mitsis EM, Bender HA, Kostakoglu L, et al. *Molecular Neurodegeneration.* 2014;9:10.

CONCLUSION

Amyloid PET imaging provided essential data that:

- Led to revised diagnoses
- Prevented initiation of incorrect or suboptimal treatment
- Avoided inappropriate referral to anti-amyloid clinical trials

Purpose: To evaluate the utility of amyloid positron emission tomography (PET) in patients typically seen in a tertiary care clinical practice for dementia evaluation

Methods

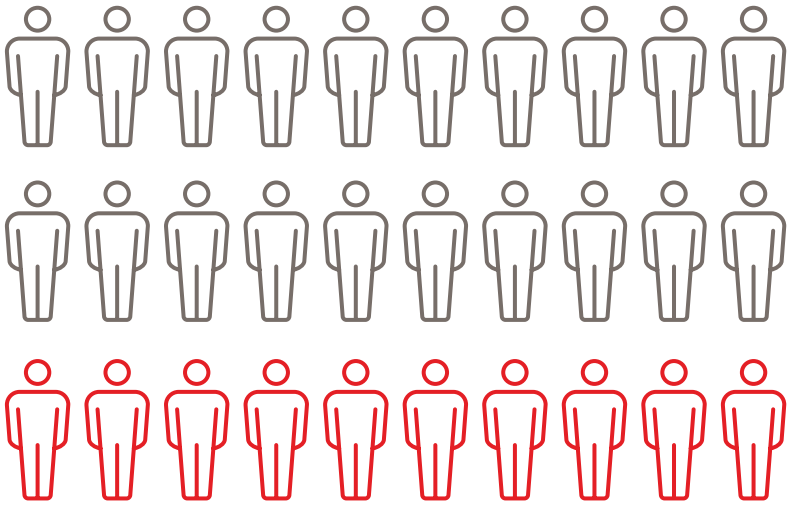
- A consecutive case series of 30 patients received amyloid PET imaging with (^{18}F) florbetapir as part of their comprehensive dementia evaluation at a large, urban dementia center
- A clinical diagnosis was made prior to patients undergoing amyloid PET imaging and revised after, as necessary

Key Results: Impact of amyloid PET imaging (N=30)

Diagnosis changed

33.3% (10 of 30)

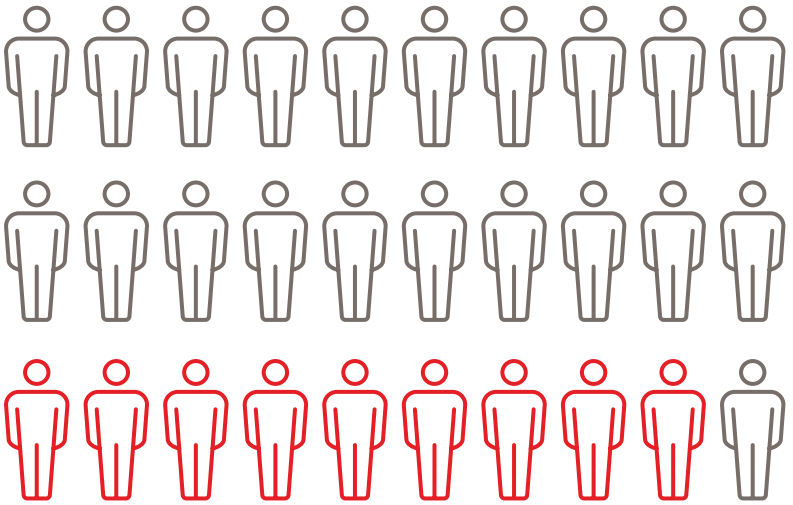
OF PATIENTS



Diagnosis clarified

30% (9 of 30)

OF PATIENTS



Impact of molecular imaging on the diagnostic process in a memory clinic

Ossenkoppele R, Prins ND, Pijnenburg YAL, et al. *Alzheimer's Dement.* 2013;9:414-421.

CONCLUSION

Combined (^{11}C) PIB and (^{18}F) FDG PET provided additional value to the standard diagnostic work-up for cognitive impairment, especially when prior diagnostic confidence is low.

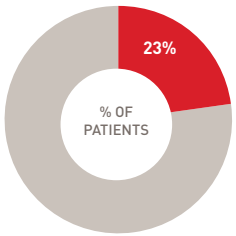
Purpose: To assess the impact of (^{11}C)Pittsburgh compound B [(^{11}C) PIB] and (^{18}F)-2-fluoro-2-deoxy-D-glucose [(^{18}F) FDG PET] on the diagnostic process in a large sample of patients from a memory clinic encompassing a wide spectrum of cognitive and/or behavioral symptoms

Methods

- 154 patients from an outpatient memory clinic underwent a standard diagnostic work-up for dementia consisting of medical history, physical and neurological examinations, laboratory tests, brain magnetic resonance imaging, and neuropsychologic testing
- Patients then underwent paired (^{11}C) PIB and (^{18}F) FDG PET and a clinical diagnosis was made by consensus of a multidisciplinary team

Key Results: Impact of amyloid PET imaging (N=154)

Change in diagnosis



- Changes occurred only when diagnostic confidence prior to amyloid PET imaging was <90

Improved diagnostic certainty (for all patients together)

Improved clinician understanding of patient's disease

81% OF PATIENTS WITH AMYLOID PET IMAGING **vs** **64%** OF PATIENTS WITH (^{18}F) FDG PET IMAGING

Effectiveness of florbetapir PET imaging in changing patient management

Pontecorvo MJ, Siderowf A, Dubois B, et al. *Dement Geriatr Cogn Disord.* 2017;44(3-4):129-143.

CONCLUSION

Access to amyloid PET imaging impacted diagnosis as well as patient management, particularly changes in AD medication.

Purpose: To evaluate the impact of amyloid positron emission tomography (PET) imaging on diagnosis and patient management of patients with cognitive impairment suspected to be related to Alzheimer's disease (AD)

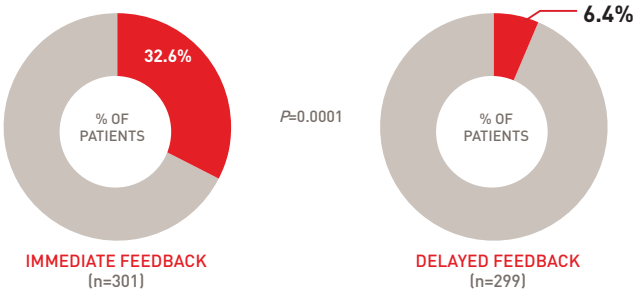
Methods

- Prospective, randomized, controlled multicenter study of 60 centers in France, Italy, and the US and including 618 patients with mild cognitive impairment or dementia for whom the cause of impairment was uncertain, but a diagnosis of AD was considered possible
- After undergoing a baseline evaluation, physicians developed a working diagnosis and management plan
- Within 30 days of completing the baseline evaluation, patients underwent amyloid PET imaging and were randomized to have their treating physician informed of the result either immediately or delayed 1-year
- Approximately 3-months after the baseline visit, the physician made any updates to the diagnosis and management plan

Key Results:

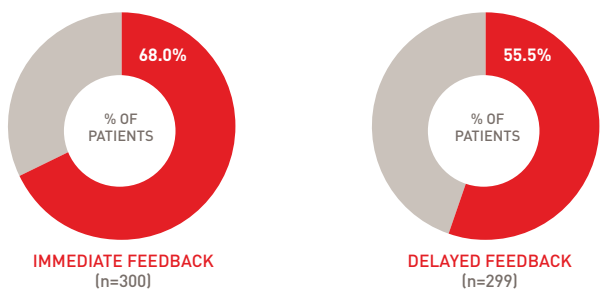
After amyloid PET imaging, significantly more patients in the immediate feedback group had a change in diagnosis compared to those in the delayed feedback group

Change in diagnosis



After amyloid PET imaging, significantly more patients in the immediate feedback had a change in management plan* compared to those receiving delayed feedback

Change in management



- **Management change was mainly driven by changes in AD medication, specifically acetylcholine esterase inhibitor use increased from a planned 43% to an actual 67% among amyloid positive patients, but decreased from a planned 35% to an actual 27% among the amyloid negative patients**

*Major diagnostic tests, initiation/cessation of medications, neuropsychological testing, diagnostic re-evaluation, specialist referral.

Incremental value of amyloid-PET versus CSF in the diagnosis of Alzheimer's disease

Ramusino MC, Garibotto V, Bacchin R, et al. *Eur J Nucl Med Mol Imaging.* 2020;47:270-280.

CONCLUSION

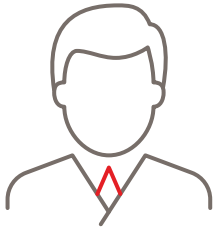
Amyloid PET imaging leads to more changes in diagnosis and greater diagnostic confidence than CSF and should be prioritized over CSF in the diagnostic workup of patients investigated for suspected AD.

Purpose: To compare the incremental value of amyloid positron emission tomography (PET) and cerebrospinal fluid (CSF) in the diagnosis of Alzheimer's disease (AD) in patients with mild cognitive impairment (MCI) or mild dementia

Methods

- Complete clinical, neurological, neuropsychological, and magnetic resonance imaging data of 71 patients in a phase 3 multicenter study were assessed by 2 dementia experts, who provided a diagnosis
- In round 1, patients were evaluated on all available information except amyloid PET and CSF results
- In round 2, diagnosis and diagnostic confidence were revised based on including either amyloid PET or CSF results in the evaluation
- In round 3, diagnosis and diagnostic confidence were revised again based on including either amyloid PET or CSF results not presented in round 2 in the evaluation

Key Results: Impact of PET imaging (N=71)



Change in diagnosis

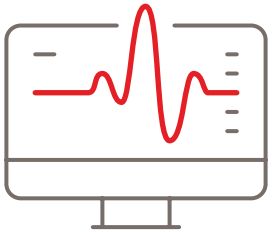
Round 2

67% CSF *P*=0.026 **100%** AMYLOID PET IMAGING

Round 3

0% CSF *P*<0.001 **78%** AMYLOID PET IMAGING

- **Among patients with an initial diagnosis of AD, a negative amyloid PET result led to significantly more diagnostic changes than a negative CSF result**



Amyloid PET results led to greater increases in diagnostic confidence than CSF results

Round 2

↑**14%** CSF *P*=0.021 ↑**21%** AMYLOID PET IMAGING

Round 3

- **Providing amyloid PET results in round 3, after CSF results were provided in round 2, further increased diagnostic confidence by +6%**
- **Providing CSF results in round 3, after amyloid PET results were provided in round 2, did not further increase diagnostic confidence**

Practical utility of amyloid and FDG-PET in an academic dementia center

Sanchez-Juan P, Ghosh PM, Hagen J, et al. *Neurology.* 2014;82:230-238.

CONCLUSION

Amyloid PET imaging had a moderate effect on clinical outcomes, with a greater effect in patients who were considered to be diagnostic dilemmas.

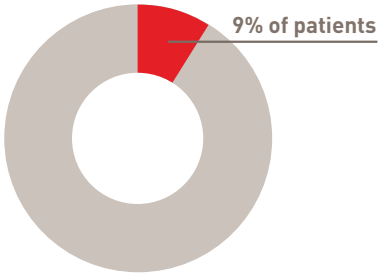
Purpose: To evaluate the effect of amyloid positron emission tomography (PET) on diagnosis and Alzheimer's disease (AD) drug treatment

Methods

- Retrospective analysis of 140 patients with cognitive impairment who had undergone amyloid PET imaging and had been assessed clinically before and after the scan
- The pre-PET clinical evaluation included an assessment by a behavioral neurologist, a caregiver interview, cognitive testing, and structural neuroimaging

Key Results: Impact of PET imaging (N=140)

Change in diagnosis



- In patients considered pre-PET diagnostic dilemmas (n=13), diagnosis changed in 38% of patients

Reduced diagnostic uncertainty

- The number of diagnostic dilemmas decreased from 19% pre-PET to 11% post-PET

Impact of beta-amyloid-specific florbetaben PET imaging on confidence in early diagnosis of Alzheimer's disease

Schipke CG, Peters O, Heuser I, et al. *Dement Geriatr Cogn Disord.* 201;33:416-422.

CONCLUSION

Even in a specialized center familiar with the diagnosis of AD, amyloid PET imaging increased diagnostic confidence and frequently influenced patient management.

Purpose: To evaluate how results from amyloid positron emission tomography (PET) imaging influence diagnosis, choice of treatment, and intended general patient management

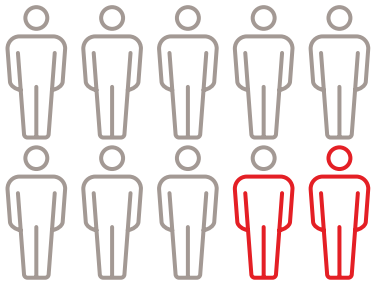
Methods

- Referring physicians whose patients received florbetaben in the context of a florbetaben phase 2b clinical trial were given a survey asking about their confidence in the initial diagnosis, significance of amyloid PET imaging results, and their anticipated future patient care
- Fourteen out of the 20 centers participating in the clinical trial returned 201 questionnaires (74% response rate)

Key Results

Almost 1 in 5 patients diagnosed with probable AD were found to be amyloid negative (n=121)

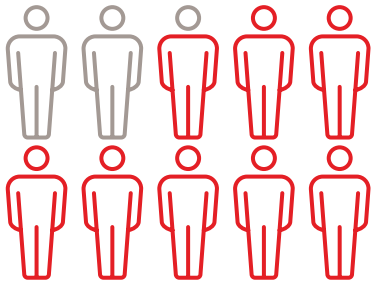
PATIENTS WHO WERE AMYLOID NEGATIVE



18% of patients

Diagnostic confidence improved in patients with probable AD who had a positive amyloid PET scan (n=99)

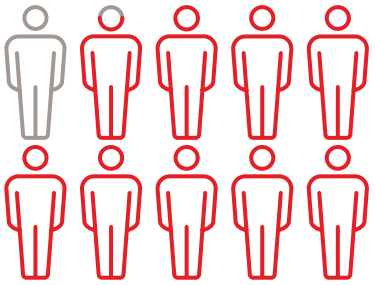
INCREASED DIAGNOSTIC CONFIDENCE



78% of patients

Physicians reported amyloid PET results would impact management of patients with probable AD (n=121)

IMPACT ON MANAGEMENT



89% of patients

Amyloid positron-emission-tomography with [^{18}F]florbetaben in the diagnostic workup of dementia patients

Schonecker S, Prix C, Raiser T, et al. *Nervenarzt.* 2017;88:156-161.
NOTE: Full text is available only in German

CONCLUSION

In patients with an unclear clinical presentation, amyloid positron emission tomography (PET) imaging can facilitate diagnosis of dementia.

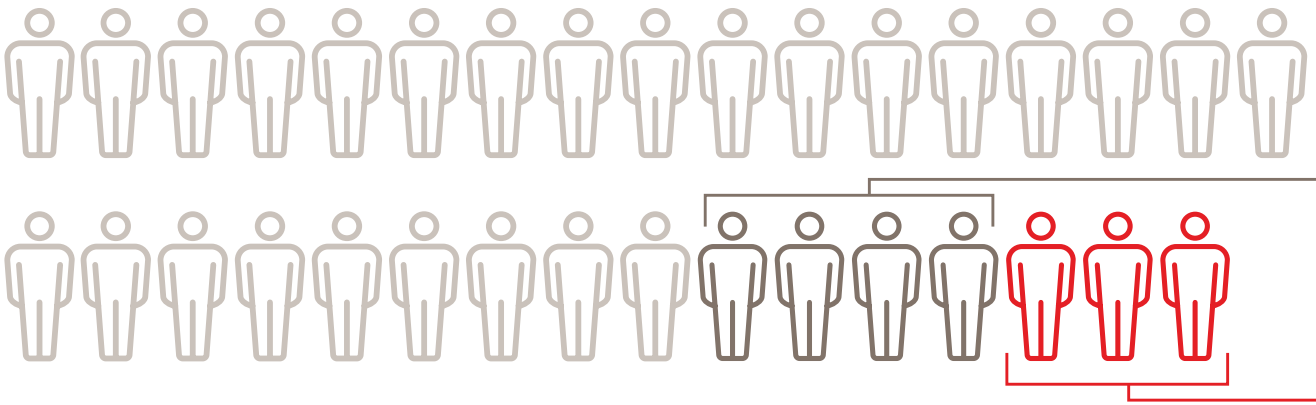
Purpose: To evaluate to what extent ^{18}F-florbetaben amyloid positron emission tomography (FBB-PET) imaging influences the diagnosis of patients with dementia

Methods

- Amyloid PET imaging with [^{18}F]-florbetaben was performed on 33 patients following a comprehensive clinical neuropsychiatric and laboratory examination, magnetic resonance imaging, and fluorodeoxyglucose-PET
- The diagnoses before and after amyloid PET imaging were compared

Key Results: Impact of amyloid PET imaging

Change in diagnosis: 7 out of 33 patients



- For 4 patients, a positive amyloid PET scan resulted in a change in diagnosis (3 to AD and 1 to cerebral amyloid angiopathy)
- For 3 patients, a negative amyloid PET scan ruled out AD

Utility of amyloid PET scans in the evaluation of patients presenting with diverse cognitive complaints

Shea Y-F, Barker W, Greig-Gusto MT, et al. *J Alzheimers Dis.* 2018;66:1599-1608.

CONCLUSION

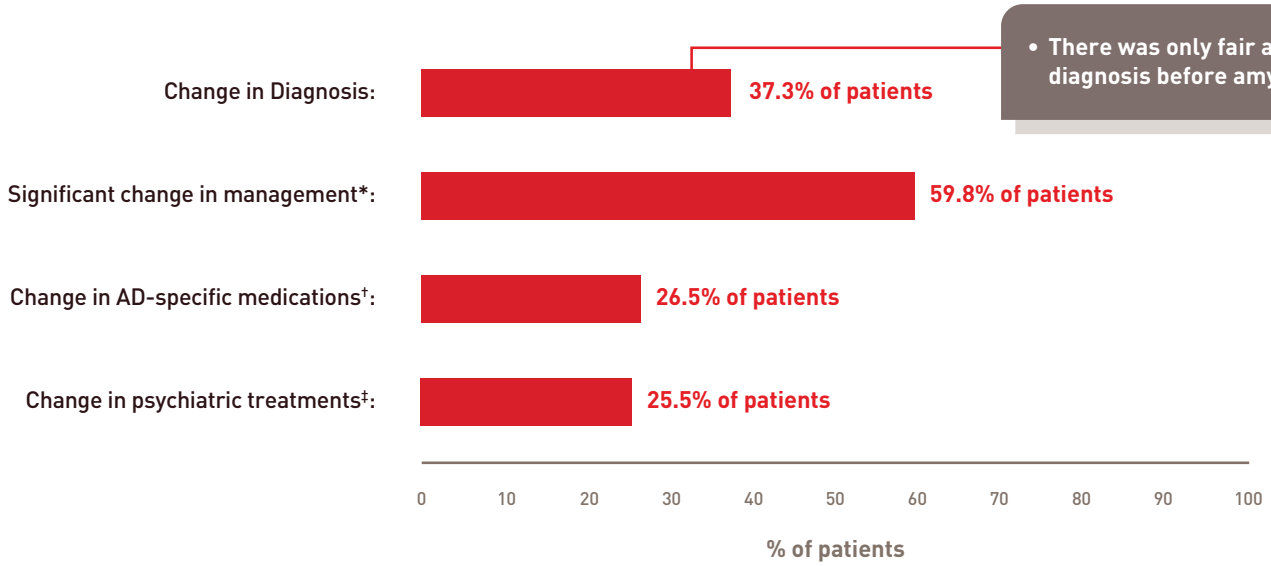
Results of amyloid PET imaging had a substantial impact on the diagnosis and management of patients with cognitive impairment.

Purpose: To evaluate the impact of amyloid positron emission tomography (PET) imaging in a "real-world" memory disorder clinic and factors making the most impact in diagnosis and management

Methods

- 102 patients with mild cognitive impairment or dementia presenting at a memory disorders clinic in Florida had a comprehensive diagnostic workup including cognitive assessments, laboratory tests, and magnetic resonance imaging to help identify the cause of their symptoms
- A neurologist established a diagnosis and management plan based on the initial assessment
- Subsequently, additional testing, including an amyloid positron emission tomography (PET) scan, was performed and any changes in diagnosis and management were made based on the results

Key Results: Impact of amyloid PET imaging (N=102)



- There was only fair agreement between the physician's diagnosis before amyloid PET imaging and after

*Includes added new medications, withdrawing medications, additional diagnostic tests, advice on daily living and safety concerns or combination of the above.

†Cholinesterase inhibitors or memantine.

‡Overall changes including antidepressants, antipsychotics, sleeping medications, and anti-epileptics.

The incremental diagnostic value of [^{18}F]florbetaben PET and the pivotal role of the neuropsychological assessment in clinical practice

Spallazzi M, Barocco F, Michelini G, et al. *J Alzheimers Dis.* 2019;67:1235-1244.

CONCLUSION

Amyloid PET imaging had greatest impact on diagnosis and confidence in patients with negative scans with an initial diagnosis of AD, and in those who were ≤65 years of age.

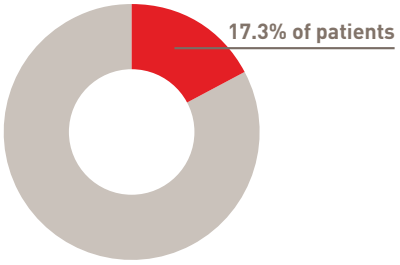
Purpose: To evaluate the impact of amyloid positron emission tomography (PET) imaging on the diagnosis of mild cognitive impairment and dementia in patients undergoing a standardized diagnostic workup that includes extensive neuropsychological assessment

Methods

- 104 patients with mild cognitive impairment (MCI) or dementia and diagnostic uncertainty underwent a complete clinical assessment, including neurological and physical examination, blood tests, magnetic resonance imaging, and a comprehensive neuropsychological assessment
- A clinical diagnosis and diagnostic confidence were established with the consensus of the neurologists at the memory clinic prior to patients undergoing amyloid PET imaging with [^{18}F]florbetaben
- Clinical diagnosis and diagnostic confidence for Alzheimer's disease (AD) or non-AD dementia were again rated after amyloid PET results were disclosed, as was the impact on the patient management plan

Key Results: Impact of PET imaging (N=104)

Change in diagnosis: 17.3%



- A negative amyloid PET scan in patients with an initial diagnosis of MCI-AD or AD (n=11) led to a change in diagnosis in 91% of patients

Improved diagnostic confidence

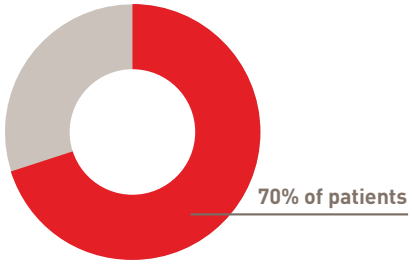
Overall, the pre-PET diagnostic confidence increased after the PET results had been disclosed (p<0.001)

PRE-PET: 69.1%

PRE-PET: 83.5%

- Impact was greater in patients ≤65 years of age and those with a negative amyloid PET scan

Change in management: 70%



- Changes may have included starting or discontinuing AD medication, change in planned care, or requests for ancillary investigations

Impact of amyloid-PET in daily clinical management of patients with cognitive impairment fulfilling appropriate use criteria

Trivino-Ibanez EM, Sanchez-Vano R, Sopena-Novales P, et al. *Medicine.* 2019;98:29(e16509).

CONCLUSION

PET imaging significantly improved diagnostic confidence and patient management in patients with cognitive improvement fulfilling clinical appropriate use criteria (AUC).

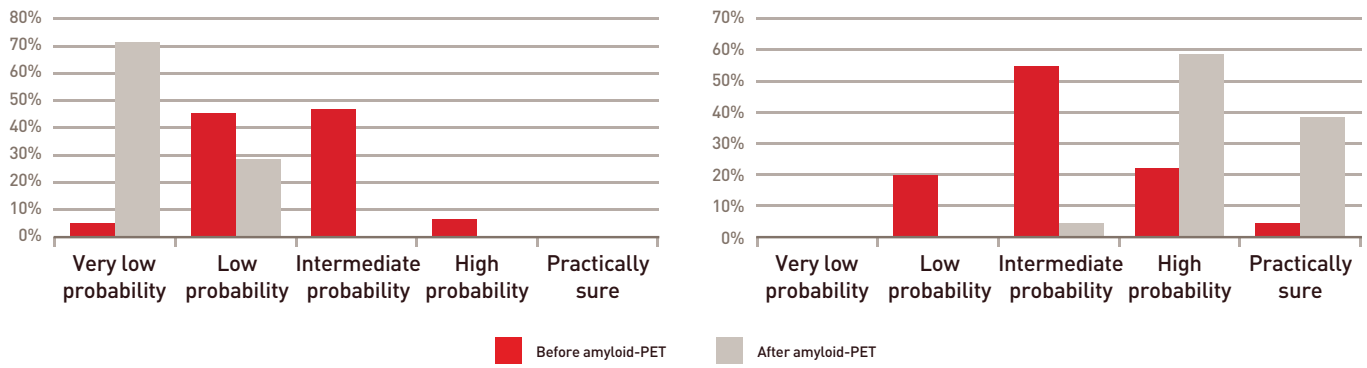
Purpose: To evaluate benefits of amyloid positron emission tomography (PET) in daily clinical management of patients with cognitive impairment fulfilling clinical AUC

Methods

- Multicenter, observational, prospective case-series study of 211 patients who fulfilled clinical AUC for amyloid PET imaging (uncertain clinical features such as early onset ≤65 years or atypical, mixed, or rapidly progressing presentation)
- Patients had an initial assessment that included history, physical and neurological examinations, cognitive assessment, and laboratory tests
- If the initial evaluation was inconclusive or insufficient for diagnosis, the patient received more specific testing with cerebrospinal fluid analysis (typically first line) or amyloid PET imaging (second line)
- For patients who had amyloid PET imaging, a neurologist re-evaluated the diagnosis (and confidence level) and treatment plan

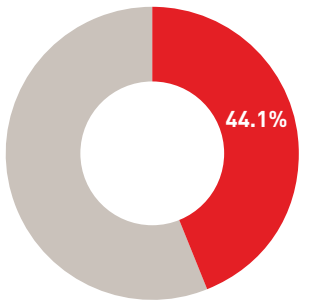
Key Results: PET imaging improved diagnostic confidence

Confidence in Alzheimer's disease (AD) diagnosis before and after amyloid PET imaging



- Neurologists were confident that 100% of patients with a negative amyloid PET scan had a "very low" (70.7%) or "low" (29.3%) probability AD
- Neurologists were confident that ~96% of patients with a positive amyloid PET scan had "high probability" (57.6%) of AD or they were "practically sure" of it (39%)

PET imaging had a high impact on patient management



- Based on amyloid PET results, 50.4% of patients who *had not* been receiving AD-specific treatment started it, and 33.8% who *had* been receiving AD-specific treatment stopped it

A more precise diagnosis by means of amyloid PET contributes to delayed institutionalization, lower mortality, and reduced care costs in a tertiary memory clinic

van Maurik IS, et al. *Alzheimers Dement*. 2022; DOI:10.1002/alz.12846.

CONCLUSION

Patients who received amyloid PET imaging as part of their diagnostic workup had a more beneficial long-term disease trajectory in terms of rates of institutionalization and mortality and lower healthcare costs

Purpose: To investigate whether adding amyloid PET to the diagnostic workup to establish a more precise diagnosis impacts long-term outcomes (healthcare costs, institutionalization, mortality) in memory clinic patients

Methods

- Consecutive patients from the Amsterdam Dementia Cohort were included, and all had a baseline visit to the Alzheimer Center Amsterdam (tertiary memory clinic based at the Amsterdam University Medical Center) between October 27, 2014, and December 31, 2016
  - All patients received a baseline diagnostic workup consisting of a standardized 1-day dementia screening including medical, neurological, and neuropsychological investigation; magnetic resonance imaging of the brain; standard laboratory work; and lumbar puncture to obtain cerebrospinal fluid
  - A clinical diagnosis was made by consensus in a multi-disciplinary meeting without knowledge of biomarkers
- Amyloid PET imaging was offered to all patients (n=1076); in total, 476 received amyloid PET and 600 did not
- Patients who accepted amyloid PET imaging and met eligibility criteria (n=449) were propensity score matched with patients without amyloid PET (n=571) and matched groups (both n=444) were compared on the rate of institutionalization, mortality, and healthcare costs in the years after diagnosis
  - Propensity score matching was used to compensate for putative selection bias based on age, gender, Mini-Mental State Examination, education, Charlson comorbidity index, availability of cerebrospinal fluid, and syndrome diagnosis

Key Results

Lower risk of institutionalization

Amyloid PET	No Amyloid PET
10% (n=45)	**21%** (n=92)

Over a 3-year period
(HR: 0.48; 0.33-0.70)

Translates to a delay of 1.5 years in 5% institutionalization

Lower mortality

Amyloid PET	No Amyloid PET
11% (n=49)	**18%** (n=81)

Over a 4-year period
(HR: 0.51; 0.36-0.73)

Corresponds with a 1.4 year longer survival after diagnosis

Lower care costs

Amyloid PET vs No Amyloid PET

- Institutional costs (largest contributor)
- General practitioner costs
- Psychological costs
- Transportation costs

Over a 4-year period

Considering institutionalization is the driving force in dementia care, even a small delay could provide tremendous potential for cost savings

Impact of amyloid PET in the clinical care of veterans in a tertiary memory disorders clinic

Vives-Rodriguez A, et al. *Alzheimers Dement*. 2022;8:e12320.

CONCLUSION

The lower-than-expected amyloid positivity rate demonstrated that, in a medically complex real-world population, the utility of amyloid PET imaging was largely found in ruling out Alzheimer's disease.

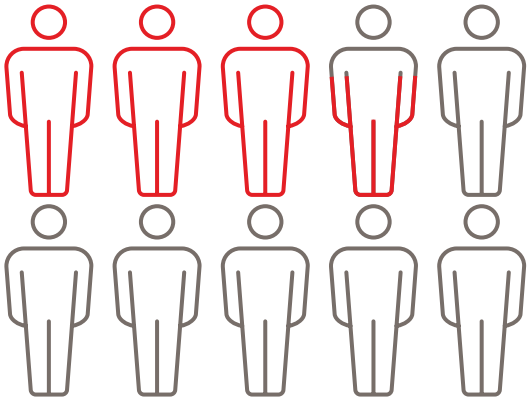
Purpose: To characterize the clinical impact of amyloid positron emission tomography (PET) imaging in the follow up of patients with cognitive decline at a tertiary VA memory disorders clinic

Methods

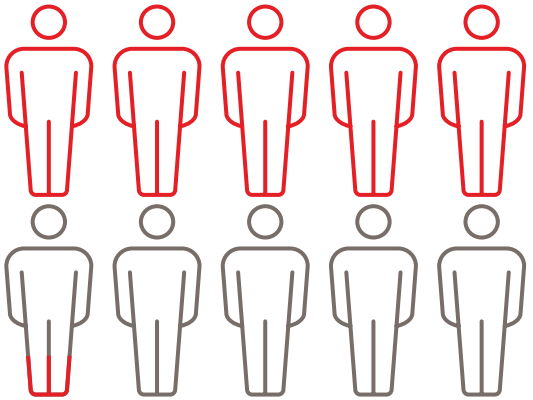
- Retrospective observational study of 197 Veterans evaluated for cognitive decline at the VA Boston Memory Disorders Clinic, a tertiary outpatient clinic that focuses on the diagnosis and treatment of patients with neurodegenerative disorders, and underwent amyloid PET imaging as part of their routine diagnostic workup
- Amyloid PET imaging could be ordered in selected cases depending on the diagnostic suspicion and indication
- Appropriate use criteria (AUC) were considered when amyloid PET studies were ordered but it was ultimately a decision of the treating clinician to order the test

Key Results: Impact of amyloid PET imaging (n=197)

Patients with a positive amyloid PET scan: 36.5% of patients



Patients with a change in diagnosis: 52.8% of patients



- **A positive scan was associated with fewer additional diagnostic tests, less diagnostic variability, more Alzheimer's disease medication prescriptions, and more research referrals**

Added value and limitations of amyloid-PET imaging: review and analysis of selected cases of mild cognitive impairment and dementia

Weidman DA, Zamrini E, Sabbagh MN, et al. *Neurocase*. 2017;23:41-51.

CONCLUSION

Amyloid PET imaging assisted dementia specialists in making a more specific diagnosis and influenced patient management.

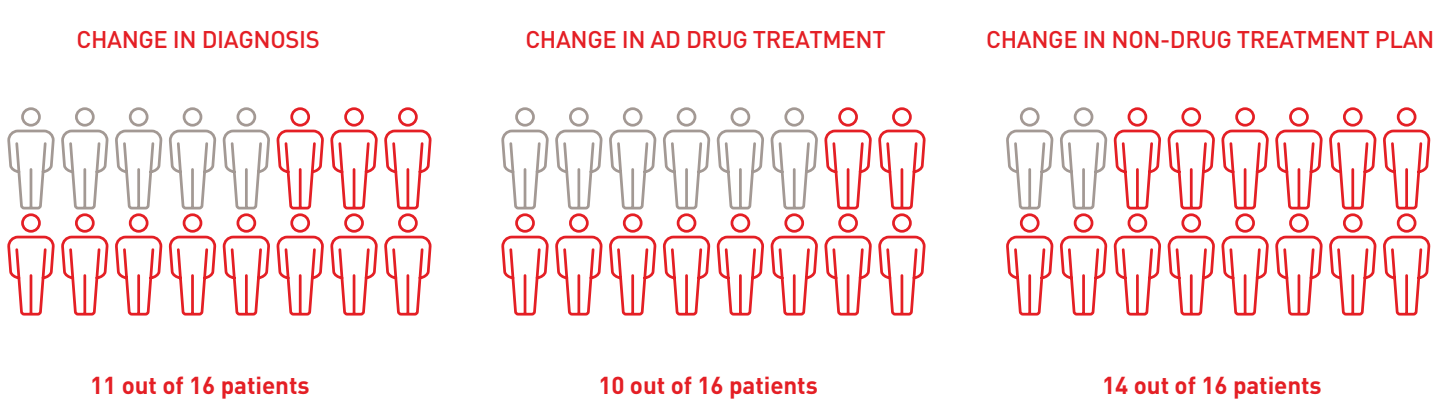
Purpose: To gain a practical understanding of the added value and limitations of amyloid positron emission tomography (PET) imaging in a clinical real-world setting

Methods

- Medical records of 16 patients with mild cognitive impairment or dementia who underwent amyloid-PET imaging were reviewed to determine whether recommended appropriate use criteria (AUC) for amyloid-PET imaging were met, a change in diagnosis was made based on amyloid PET results, diagnostic confidence increased, and whether there were changes in drug treatment

Key Results

Impact of amyloid PET imaging (N=16)



- **Changes may have included referral to, discussion of, or withdrawing consideration of a research trial; disease-specific education and counseling and supportive therapy; focus back on psychiatric care, career and future planning, and safety; and cancellation of other diagnostic tests**

Diagnosing dementia in the clinical setting: can amyloid PET provide additional value over cerebrospinal fluid?

Weston PSJ, Paterson RW, Dickson J, et al. *J Alzheimers Dis.* 2016;54:1297-1392.

CONCLUSION

Amyloid PET provided added diagnostic value in cases where cerebrospinal fluid (CSF) results were borderline and diagnostic uncertainty remained.

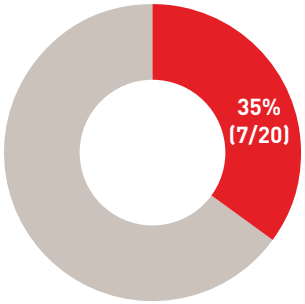
Purpose: To determine in a real life clinical setting whether amyloid positron emission tomography (PET) can provide additional diagnostic value beyond CSF measurement alone

Methods

- 20 patients with dementia were evaluated by an experienced cognitive neurologist using neuropsychological testing, magnetic resonance imaging, and lumbar puncture
- Physicians gave an initial diagnosis and degree of diagnostic certainty
- Patients then underwent amyloid PET imaging and physicians were again asked to give a diagnosis/diagnostic certainty based on the results of the scan

Key Results: Impact of amyloid PET imaging (N=20)

Change in diagnosis: 35% of patients

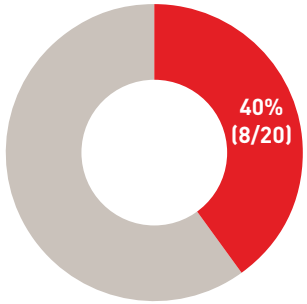


Improved diagnostic certainty:

PRE-PET: 68% certainty

POST-PET: 84% certainty

Change in management: 40% of patients



Impact of ^{18}F-florbetapir PET imaging of β-amyloid neuritic plaque density on clinical decision-making

Zannas AS, Doraiswamy PM, Shpanskaya KS, et al. *Neurocase.* 2014;20:466-473.

CONCLUSION

Both positive and negative amyloid PET scans enhanced diagnostic certainty and impacted clinical decision-making.

Purpose: To evaluate how amyloid positron emission tomography (PET) impacts clinical decision making in patients with cognitive impairment

Methods

- A series of 11 patients who had progressive cognitive decline suspected to be caused by Alzheimer's disease (AD) and had undergone standard clinical, laboratory, and cognitive evaluations, along with amyloid PET imaging with 18F-florbetapir, is presented
- Each patient had received a diagnosis and treatment plan before the amyloid PET scan was performed
- After the amyloid PET scan, the result was disclosed to the physician and the physician documented intended changes in diagnosis and the treatment plan

Key Results: Impact of amyloid PET imaging

Improved diagnostic certainty

- **While 4 patients had an indeterminate diagnosis prior to the amyloid PET scan, only one case remained indeterminate after the scan**

Patients with negative amyloid PET scans

- **Diagnosis changed in 4 out of 5**
- **Treatment plan changed in 2 out of 5**

Patients with positive amyloid PET scans

- **Diagnosis changed in 4 out of 6**
- **Treatment plan changed in 3 out of 6**

Diagnostic value of amyloid imaging in early onset dementia

Zwan MD, Bouwman FH, Van Der Flier W, et al. *Alzheimers Dement.* 10:2014:14.

CONCLUSION

Amyloid PET imaging resulted in changes in the diagnostic work-up of patients with early onset dementia, improved the physicians' diagnostic confidence, and changed patient management, particularly as a result of a negative scan.

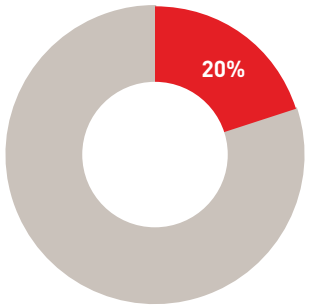
Purpose: To evaluate the diagnostic value of amyloid positron emission tomography (PET) in assessing patients with early onset dementia

Methods

- 80 patients with early onset dementia (<70 years) and physician diagnostic confidence <90% after a full routine diagnostic workup for dementia underwent a [^{18}F]flutemetamol PET scan
- Clinical diagnosis, confidence in the diagnosis, and management plan were determined before and after the results of the amyloid PET scan were disclosed

Key Results: Impact of amyloid PET imaging (N=80)

Change in diagnosis: 20% of patients

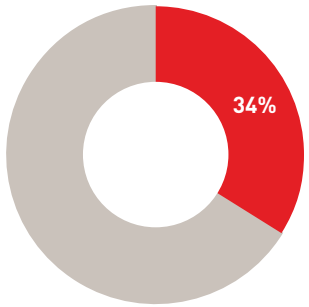


Improved diagnostic confidence:

PRE-PET: 76% certainty

POST-PET: 90% certainty

Change in management: 34% of patients



Quantitative appraisal of the amyloid imaging taskforce appropriate use criteria for amyloid-PET

Altomare D, Ferrari C, Festari C, et al. *Alzheimers Dement.* 2018;14:1088-1098.

CONCLUSION

Use of amyloid PET imaging in patients who did not meet AIT criteria was associated with clinical utility similar to that observed in patients who did meet AIT criteria.

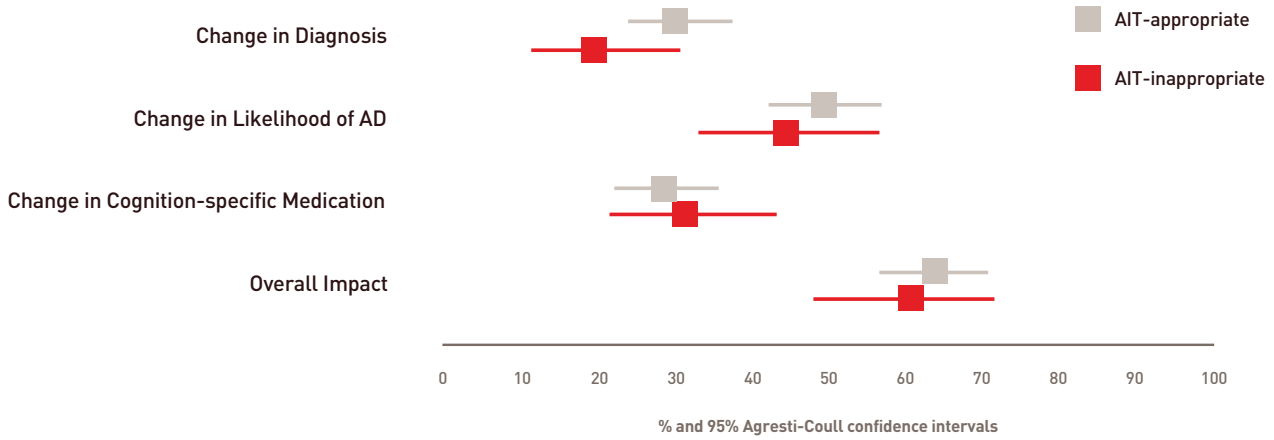
Purpose: To test the hypothesis that amyloid positron emission tomography (PET) use based on the Amyloid Imaging Taskforce (AIT) criteria had greater utility than in cases that did not meet AIT criteria

Methods

- 171 AIT-appropriate* and 67-AIT-inappropriate† patients who were enrolled in a multicenter study and underwent amyloid PET imaging after completing a comprehensive diagnostic workup (including clinical and neuropsychological assessment, structural imaging, and potentially fluorodeoxyglucose-PET and cerebrospinal fluid measurements of amyloid or tau) were retrospectively identified
- Based on all test results other than amyloid PET imaging, physicians formulated a diagnosis, diagnostic likelihood that cognitive impairment was due to Alzheimer's disease (AD), and therapeutic plan
- Physicians were then asked to reformulate the same outcomes based on the additional consideration of the amyloid PET result

Key Results: Amyloid PET imaging demonstrated similar clinical utility in AIT-appropriate and AIT-inappropriate patients‡

Outcomes of clinical utility in AIT-appropriate and AIT-inappropriate patients



*Unexplained mild cognitive impairment, >65 years of age with possible AD but unusual presentation, young-onset dementia (<65 years of age).

†Probably AD and typical age (>65 years of age), subjective cognitive decline, no diagnostic uncertainty, no impact expected (dementia with Lewy bodies).

‡As assessed by the overlap of the 95% Agresti-Coull confidence intervals.

Critical review of the appropriate use criteria for amyloid imaging: effect on diagnosis and patient care

Apostolova LG, Haider JM, Goukasian N, et al. *Alzheimers Dement* (Amst). 2016;5:15-22.

CONCLUSION

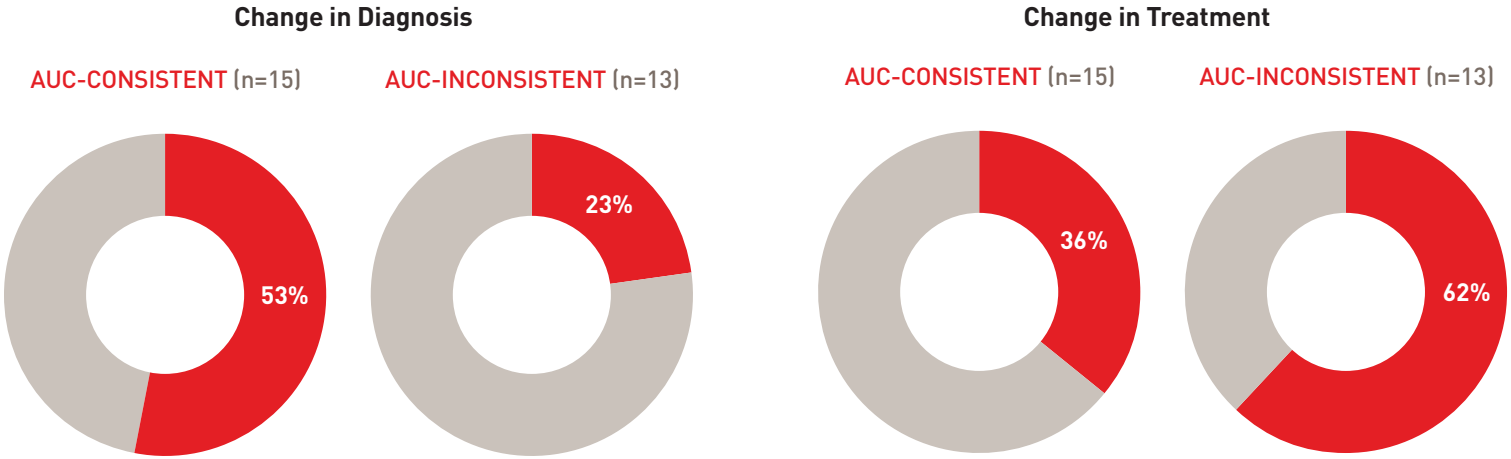
Results suggest that patients who did not fall within the AUC were no less likely to benefit from amyloid imaging than patients meeting AUC.

Purpose: To examine the utility of the Appropriate Use Criteria (AUC)* for amyloid imaging in evaluation of cognitive impairment

Methods

- 53 patients with cognitive impairment who received amyloid PET imaging for diagnostic purposes at a US tertiary medical center were classified as early onset (cognitive decline began before 65 years of age) or late onset (cognitive decline began after 65 years of age), as well as AUC-consistent or AUC-inconsistent*

Key Results: Impact of amyloid PET imaging



*AUC includes (1) patients with progressive mild cognitive impairment 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.

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

De Wilde A, Ossenkoppele R, Pelkmans W, et al. *Alzheimers Dement.* 2019;15:1458-1467.

CONCLUSION

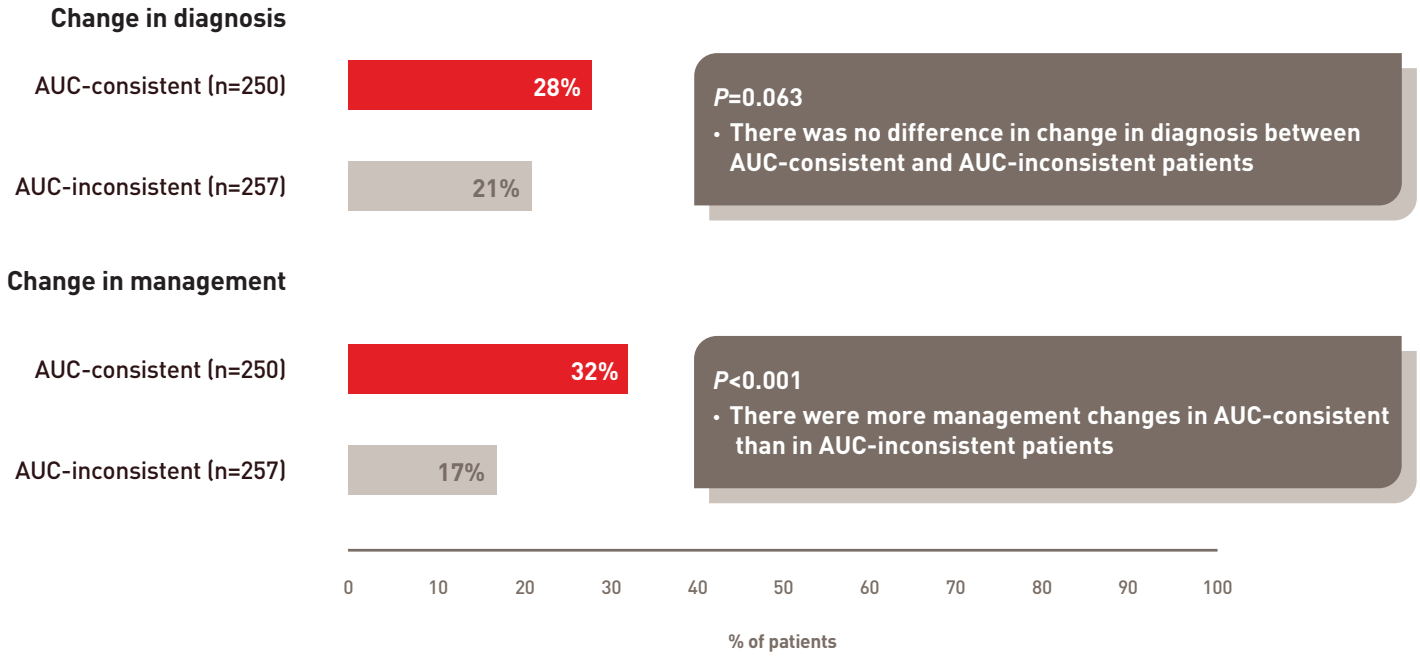
In both AUC-consistent and AUC-inconsistent patients, amyloid PET imaging led to substantial changes in diagnosis and management.

Purpose: To evaluate the usefulness of the appropriate use criteria (AUC) for amyloid positron emission tomography (PET) imaging in an unselected memory clinic cohort

Methods

- As part of the Alzheimer Biomarkers In Daily practice (ABIDE) project, 507 patients underwent a standard diagnostic dementia evaluation consisting of medical history, informant-based history, neurological examinations, neuropsychological testing, basic laboratory testing, magnetic resonance imaging, and were offered amyloid PET imaging
- AUC was retrospectively examined and patients were classified as AUC-consistent* (n=250) or AUC-inconsistent† (n=257)
- Post-PET changes in diagnosis and management were compared between the 2 groups

Key Results: Impact of amyloid PET imaging



*Persistent or progressive unexplained mild cognitive impairment, possible Alzheimer's disease but unclear clinical presentation, or patients with progressive dementia at a young age of onset (<65 years).

†Subjective cognitive decline, AD not suspected as a primary or alternative etiology, or confidence in AD as suspected etiology was <15%.

Effect of amyloid imaging on the diagnosis and management of patients with cognitive decline: impact of appropriate use criteria

Grundman M, Johnson KA, Lu M, et al. *Dement Geriatr Cogn Disord.* 2016;41:80-92.

CONCLUSION

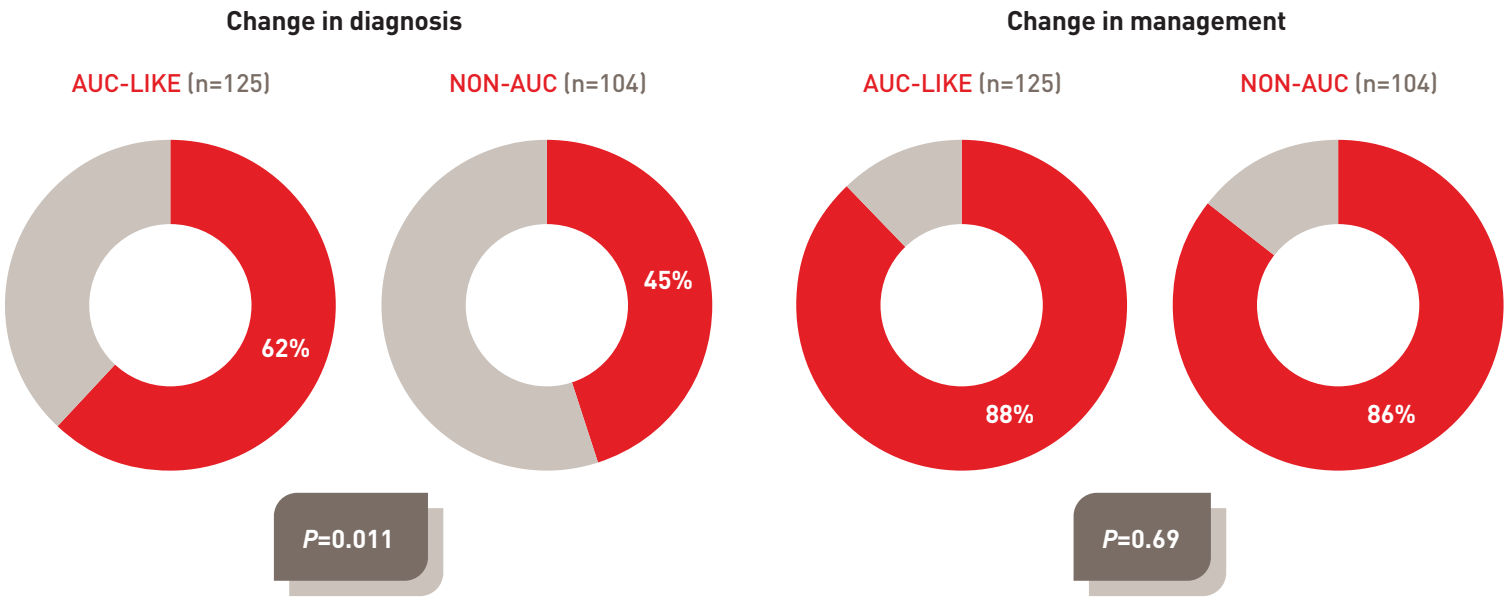
Amyloid PET imaging results altered diagnostic thinking and management in both AUC-like and non-AUC patients, although they tended to be modestly higher in AUC-like patients.

Purpose: To compare the impact of amyloid positron emission tomography (PET) on diagnosis and management in patients likely to either meet or not meet appropriate use criteria* (AUC)

Methods

- An additional analysis of data acquired in a prior study designed to examine the impact of amyloid PET imaging on intended patient management was conducted
- The prior study included 229 patients with a history of cognitive decline and uncertain diagnosis who were evaluated (without the use of amyloid PET imaging) for the underlying cause of the decline
- Physicians recorded a working diagnosis for each patient, along with a diagnostic testing and management plan, before and after an amyloid PET scan was performed and the results were compared
- The present study extended the analysis to patients having a profile consistent with AUC (AUC-like) or inconsistent with AUC (non-AUC)

Key Results: Impact of amyloid PET imaging



*Those with persistent unexplained mild cognitive impairment, those satisfying core criteria for possible Alzheimer's disease with unclear clinical presentation, and those with dementia and atypically early onset.

Amyloid imaging for differential diagnosis of dementia: incremental value compared to clinical diagnosis and [^{18}F]FDG PET

Hellwig S, Frings L, Bormann T, et al. *Eur J Nucl Med Mol Imaging.* 2019;46:312-323.

CONCLUSION

There was no significant difference between the percentages of AUC-consistent and AUC-inconsistent patients who had a change in diagnosis following amyloid PET imaging.

Purpose: To evaluate the incremental diagnostic value of amyloid positron emission tomography (PET) in addition to clinical diagnosis and [^{18}F]FDG PET in a real-life memory clinic population

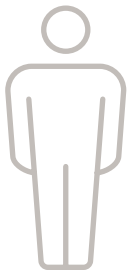
Methods

- 138 patients with cognitive impairment of uncertain etiology (complicated presentation) were referred for diagnostic imaging with amyloid PET imaging and [^{18}F]FDG PET
- Dementia experts determined a baseline diagnosis based on comprehensive clinical assessment and [^{18}F]FDG PET results, but not considering amyloid PET imaging results
- Of the 138 patients, 84 were diagnosed with neurocognitive disorders and were assigned to the following subgroups: 1) Alzheimer's Disease (AD); 2) dementia with Lewy bodies (DLB); 3) fontotemporal dementia (FTD); or 4) non-neurodegenerative (NND) causes of major neurocognitive disorder (ie, alcohol-related dementia, vascular dementia, normal pressure hydrocephalus, psychiatric disorders)
- Results of amyloid PET imaging was disclosed to the dementia experts and they were asked to adjust their former diagnoses as necessary

Key Results: Impact of amyloid PET imaging

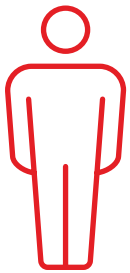
Change in diagnosis

LATE ONSET AUC-CONSISTENT (n=33)



21%
of patients

LATE ONSET AUC-INCONSISTENT (n=15)



27%
of patients

AUC=appropriate use criteria.

Amyloid PET ordering practices in a memory disorders clinic

Turk KW, Vives-Rodriguez A, Schiloski KA, et al. *Alzheimers Dement*. 2022;8:e12333.

CONCLUSION

Almost all patients who underwent amyloid PET imaging, and almost 2/3 of those who did not, met AUC. These results demonstrated that specialty-trained clinicians use both clinical judgment and AUC in determining when to order scans, rather than indiscriminately ordering them.

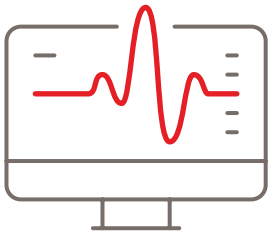
Purpose: To assess amyloid positron emission tomography (PET) ordering practices in a tertiary VA memory disorders clinic and adherence to appropriate use criteria (AUC) in order to determine how often clinicians might order it if covered by insurance in the future

Methods

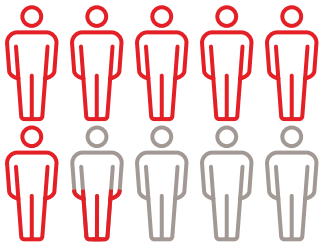
- 570 Veterans were evaluated for cognitive decline at the VA Boston Memory disorders clinic, a tertiary outpatient clinic that focuses on the diagnosis and treatment of patients with neurodegenerative disorders, from October 2016 to January 2020
- Routine diagnostic workup included clinical history and exam, brain imaging (magnetic resonance imaging or computed tomography), blood work, and a comprehensive cognitive battery
- After this evaluation, additional testing, including amyloid PET imaging, could be ordered in selected cases depending on the diagnostic suspicion and indication
- AUC were considered when amyloid PET studies were ordered, but it was ultimately a decision of the treating clinician to order the test

Key Results:

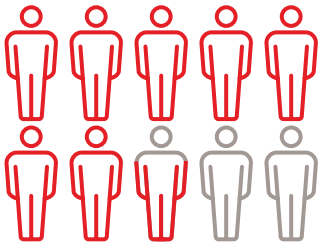
Amyloid PET imaging ordered as part of routine diagnostic workup (n=565): 34.9% of patients



Patients who did not undergo amyloid PET imaging but met AUC (n=326): 64.4%



Overall percentage of memory clinic patients who met AUC: 77%



- **98% of amyloid PET scans met AUC**
- **Patients who underwent amyloid PET imaging were younger (69.6 years vs 76.0 years) and more frequently in the mild cognitive impairment stage (64.6% vs 51.4%) than dementia stage (33.3% vs 38.0%), compared to those who did not**
- **Alzheimer's disease (AD) as the etiological clinical diagnosis was more common among patients who underwent amyloid PET imaging than those who did not (61.5% vs 42.9%)**

Published demonstrations of amyloid PET utility within drug development trials

Initial adoption

In Expedition 1, an early clinical trial for the experimental anti-amyloid agent solanezumab, amyloid PET was not used to identify patients for inclusion. As a result, approximately 25% were later found to not have evidence of amyloid-related disease. Following these learnings, subsequent trials for solanezumab and others incorporated amyloid PET into their protocols.

Patient identification

Amyloid PET has become incorporated into drug development studies to support appropriate patient identification, with considerable published literature [8 publications] supporting its use.

Additional utility

Amyloid PET has also proven to be effective for monitoring amyloid-reduction therapeutics and assessing their ability to reduce neuritic amyloid plaques.

The publications listed below demonstrate the clinical utility of amyloid PET in drug development trials that employed Amyvid PET imaging as part of their protocol.

Brody M, Liu E, Di J, et al. A phase II, randomized, double-blind, placebo-controlled study of safety, pharmacokinetics, and biomarker results of subcutaneous bapineuzumab in patients with mild to moderate Alzheimer's disease. *J Alzheimers Dis.* 2016;54(4):1509-1519.

Cummings JL, Zhong K, Kinney JW, et al. Double-blind, placebo-controlled, proof-of-concept trial of bexarotene X in moderate Alzheimer's disease. *Alzheimers Res Ther.* 2016;8:4.

Fleisher AS, Joshi AD, Sundell KL, et al. Use of white matter reference regions for detection of change in florbetapir positron emission tomography from completed phase 3 solanezumab trials. *Alzheimers Dement.* 2017;13(10):1117-1124.

Honig LS, Vellas B, Woodward M, et al. Trial of solanezumab for mild dementia due to Alzheimer's disease. *N Engl J Med.* 2018;378(4):321-330.

Lowe SL, Duggan Evans C, Shcherbinin S, et al. Donanemab (LY3002813) phase 1b study in Alzheimer's disease: rapid and sustained reduction of brain amyloid measured by Florbetapir F18 imaging. *J Prev Alzheimers Dis.* 2021;8(4):414-424.

Michelson D, Grundman M, Magnuson K, et al. Randomized, placebo controlled trial of NPT088, a phage-derived, amyloid-targeted treatment for Alzheimer's disease. *J Prev Alzheimers Dis.* 2019;6(4):228-231.

Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in early Alzheimer's disease. *N Engl J Med.* 2021;384(18):1691-1704.

Salloway S, Honigberg LA, Cho W, et al. Amyloid positron emission tomography and cerebrospinal fluid results from a crenezumab anti-amyloid-beta antibody double-blind, placebo-controlled, randomized phase II study in mild-to-moderate Alzheimer's disease (BLAZE). *Alzheimers Res Ther.* 2018;10(1):96.