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Use of Amyloid Positron-Emission Tomography to Diagnose Alzheimer's Disease in Clinical Practice in South Korea: Expert Recommendations

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Amyloid positron-emission tomography (PET) is the optimal method for detecting amyloid plaque deposition in patients experiencing cognitive decline, which is essential for diagnosing Alzheimer's disease. However, its clinical application globally has been restricted by the high cost, short radiotracer half-life, and significant accessibility challenges. In particular, the lack of treatment options following diagnosis has been considered the largest obstacle to using amyloid PET as a diagnostic tool. Consequently, the current appropriate-use recommendations for amyloid PET tend to support restricting its use. However, the relatively low cost and superior accessibility of amyloid PET in South Korea have resulted in it being used much more frequently in clinical settings than in other countries. The recent introduction of disease-modifying drugs has increased the importance and frequency of amyloid PET usage. Considering these circumstances, this article presents expert opinions on the appropriate use of amyloid PET in South Korea based on existing recommendations and survey results from dementia experts in South Korea.

Keywords Alzheimer's disease; mild cognitive impairment; amyloid; positron-emission tomography; guidelines; South Korea.

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INTRODUCTION

The latest estimates suggest that more than 55 million people currently live with dementia worldwide, and this number is predicted to increase to about 78 million by 2030 and to 139 million by 2050.[1,2] The increasingly aged population in South Korea has resulted in the prevalence and incidence of dementia increasing substantially in recent years, notably among older age groups (≥65 years), and this trend is expected to continue until 2050 and beyond.[3-7] A recent national epidemiological analysis in South Korea estimated that more than 786,000 people had dementia in 2021.[7]

Alzheimer's disease (AD) is a continuum from pathophysiological, biomarker, and clinical perspectives, in which pathology can be present without any symptoms (Table 1).[8-14] In brief, patients can experience self-reported subjective complaints, defined as subjective cognitive decline (SCD), which is regarded as a preclinical stage of AD, but not all cases of SCD develop into AD. Overt AD dementia is preceded by mild cognitive impairment (MCI) in many cases.[15]

Amyloid-beta (Aβ) peptide plaques are a key neuropathological hallmark of AD and an important diagnostic marker for both AD-related MCI and dementia. Amyloid positron-emission tomography (PET) is a reliable in vivo tool for detecting amyloid plaques in AD.[13,16-19] The use of amyloid PET as a diagnostic tool for AD is gradually increasing. The

Table 1. Brief definitions of AD and related conditions associated with the AD spectrum, from CU to AD dementia

Syndrome	Definition
CU	Cognitive performance in the nonimpaired range for that individual based on all available information, defined as not MCI or dementia. A subset of CU individuals may self-report SCD (see below) and/or demonstrate subtle decline on serial cognitive testing.[8]
SCD	A preclinical condition with self-reported experience of worsening or more frequent confusion or memory loss and with normal performance on objective neuropsychological tests.[9] SCD is a heterogeneous condition mixed with AD and non-AD related conditions. It is currently unclear whether baseline amyloid or tau pathology in SCD can predict progression to AD dementia.[10]
MCI	Cognitive performance is below the expected range for that individual based on all available information. This may be based on clinical judgement and/or cognitive test performance. Additionally, evidence of decline in cognitive performance from baseline is required. Although cognitive impairment is the core clinical criteria, neurobehavioral changes (e.g., mood, anxiety or motivation) may be a prominent feature of the clinical presentation. The individual performs daily life/functional activities independently but, whilst not demented, cognitive difficulty may result in a detectable but mild functional impact on more complex activities of daily life.[8,11,14]
Alzheimer's clinical syndrome	Previously referred to as "possible or probable AD." A clinical syndrome meeting the core clinical criteria for cognitive deficits for AD dementia, but either 1) has a sudden onset of impairment or demonstrates insufficient historical detail or objective documentation of progression, or 2) has an etiologically mixed presentation because of evidence of vascular or Lewy pathology.[8,12]
AD dementia	Substantial progressive cognitive impairment that affects several domains and/or neurobehavioral symptoms, resulting in a clear functional impairment on daily life. The individual is no longer fully independent and requires assistance with daily life activities. This is the primary feature differentiating AD dementia from MCI. Specifically, AD dementia is characterized by the presence of two types of protein aggregates: 1) amyloid plaques composed of β-amyloid protein and 2) neurofibrillary tangles composed of tau protein.[8,13]

AD, Alzheimer's disease; CU, cognitively unimpaired; MCI, mild cognitive impairment; SCD, subjective cognitive decline.

technique is also useful for the differential diagnosis of disorders causing dementia and for guiding changes in clinical management.[20-26] While clinical judgment—including performing neurological examinations and focusing on clinical symptoms—is essential for diagnosing AD, a recent Bayesian meta-analysis that included 5,967 patients enrolled in 48 studies showed that amyloid PET had a high sensitivity (0.91) and specificity (0.81) for differentiating AD from normal controls.[27] Moreover, although there is no correlation between the degree of amyloid deposition and the severity of AD, confirming the presence of amyloid pathology is essential for diagnosing AD.[28,29] Amyloid PET can be used to make both qualitative and quantitative assessments.[29]

Amyloid PET tracers enable the accurate detection of amyloid plaques in AD. Three amyloid PET radiotracers (^{18}F-florbetaben, ^{18}F-flutemetamol, and ^{18}F-florapronol) are approved in South Korea for use in amyloid PET for evaluating AD.[30] Two of these (^{18}F-florbetaben and ^{18}F-flutemetamol) are also approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for amyloid imaging for clinical use, and both of these regulatory authorities have also approved ^{18}F-florbetapir.[19,31] Among the three radiotracers approved in South Korea, the ability to discriminate between positive and negative images was found to be highest for ^{18}F-flutemetamol PET (with an area under the receiver operating characteristic curve [AUC] of 0.989), followed by ^{18}F-florbetaben PET (AUC=0.978) and then ^{18}F-florapronol PET (AUC=0.901).[30] A high level of concordance (91.4%) was reported for amyloid positivity between ^{18}F-florbetaben and ^{18}F-florapronol PET in patients with cognitive impairment.[32]

The effective radiation dose of amyloid PET has been demonstrated to be within the safe range. For example, ^{11}C-Pittsburgh Compound-B PET yields an average dose of 4.74 mSv, comparable with that of other PET tracers used in brain studies.[33] Additionally, assessments of ^{18}F-based amyloid PET by the Korean National Evidence-Based Healthcare Collaborating Agency indicated that doses below 20 mSv pose no significant health risks.[34] Nevertheless, further research is needed, and a wider discussion is beyond the scope of the current article.

However, there are also limitations to amyloid PET. One limitation is that it only visualizes dense amyloid plaques, and not amyloid oligomers that mediate multiple pathogen-

ic mechanisms in AD that lead to neurotoxicity.[35] Furthermore, the presence of amyloid is not an exclusive feature of AD, since 10%−30% of cognitively normal older individuals and patients with other neurodegenerative disorders show amyloid PET positivity.[19,36-41] Another drawback of amyloid PET is its expense, and there are conflicting opinions about its cost-effectiveness in early-stage AD.[42,43]

Therefore, over the last decade, to avoid indiscriminate use and encourage appropriate utilization of amyloid PET, recommendations for its appropriate use have been published.

In 2013, a set of appropriate-use criteria for amyloid PET scans was developed by the Amyloid Imaging Task Force (AIT), convened by the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the Alzheimer's Association (AA),[44] which have been used to inform guidelines in Canada,[45] the UK,[46] and Italy[47]; Spanish guidelines have also been developed.[48,49]

However, the situation in South Korea regarding the use of amyloid PET in AD is different from that in many other countries due to several factors. First, in contrast to many other countries that require referral by a primary care physician, amyloid PET is highly accessible in South Korea—patients can request an amyloid PET scan at any time by going directly to a dementia clinic. Second, affordability—amyloid PET is less expensive in South Korea than in other countries with a cost of USD 500−900 per scan. Third, willingness to have a scan—a 2022 Gallup survey of 1,006 South Korean people conducted in association with the Korean Dementia Association, found that 60.4% were willing to take amyloid PET when experiencing worse memory loss than previously (unpublished data, Park et al., 2022). Fourth, the infrastructure is favorable in South Korea, with PET scans being widely available. As at 2022, PET scanners were available in 142 specialist centers in South Korea, and more than 10,000 amyloid PET scans were conducted in the real-world clinical setting rather than for research purposes. In contrast, amyloid PET in the US is restricted to research settings—it is not yet part of standard clinical practice due to it not being covered by Medicare or other insurers.[50] In addition, the resources available for AD diagnosis and treatment vary among European countries, including the capacity for performing amyloid PET scans and the number of dementia specialists.[51,52]

The IDEAS (Imaging Dementia−Evidence for Amyloid Scanning) study showed that the use of amyloid PET was associated with changes in the clinical management of patients with MCI or dementia of uncertain etiology.[25] The introduction of disease-modifying therapy (DMT) for MCI and early AD will impact the use of amyloid PET. In particular, the FDA approval of anti-amyloid DMTs such as lecanemab[53] will increase the clinical use of amyloid PET.[19] This situation indicates the need for new South Korean expert recommendation for amyloid PET that are tailored to the changing AD treatment environment and South Korea's unique situation regarding dementia management.

The aim of this article is to provide guidance to dementia care practitioners regarding the types of patients and clinical circumstances in which amyloid PET should be used in South Korea. The guidance was developed using the consensus opinions of dementia experts in South Korea, based on previously published expert recommendation in other countries for the use of amyloid PET in AD, and on the results of a commissioned survey of South Korean physicians specializing in dementia.

METHODS

Consensus/expert opinion

Six neurology specialists with considerable experience in treating AD patients in South Korea provided their opinions on the use of amyloid PET in diagnosing cognitive impairment and AD. The opinions were based on the clinical experience of experts, the survey findings, and previous guidelines for the use of amyloid PET in AD that included the AIT in the US,[44] the Specialized Task Force on Amyloid Imaging in Canada,[45] the UK Intercollegiate Standing Committee on Nuclear Medicine guidelines,[46] the Italian Interdisciplinary Working Group,[47] and the Spanish SEMNIM consensus guidelines.[48,49] The South Korean expert recommendations were derived after four rounds of discussion, which included virtual meetings (Supplementary Fig. 1 in the online-only Data Supplement).

Survey on the use of amyloid PET in South Korea

A survey on the current use of amyloid PET to diagnose cognitive impairment (SCD and MCI) and AD was completed by 59 physicians specializing in dementia during November 2022. The survey comprised 51 questions, to which respondents provided written answers (Supplementary Table 1 in the online-only Data Supplement).

Survey results

Most of the 56 respondents were neurologists (60.7%, *n*=34), and the rest were psychiatrists (39.3%, *n*=22). Most respondents (46/53, 86.8%) worked in tertiary hospitals with >500 beds, and the remainder in general hospitals with ≥100 and <500 beds (*n*=6, 11.3%) or smaller hospitals with ≥30 to <100 beds (*n*=1, 1.9%). The respondents indicated that amyloid PET scans were available in most of these hospitals (94.6%, 53/56). Over half of the respondents (54.7%, 29/53) treated ≥200 patients for cognitive impairment each month,

commonly with mild-to-moderate dementia (77.4%, 41/53) or MCI (60.4%, 32/53).

Fifty-two of the respondents most commonly performed ≥5 to <10 amyloid PET scans/month (32.7%), followed by <5 scans/month (26.9%) and >20 scans/month (17.3%). The main reasons for performing amyloid PET scans were clinical evidence (76.9%), high test accuracy (75.0%), and the reliability of the analysis/interpretation of results (48.0%).

In general, the survey results showed that dementia experts in South Korea comply with the preconditions stated in the appropriate use recommendations (AUR) of the AIT in the US[44]: most respondents did not conduct amyloid PET scans without previously performing neuropsychological tests (3.9% rarely and 88.5% never), and most respondents always (44.2%, 23/52) or sometimes (50.0%, 26/52) performed an amyloid PET scan when they considered that the presence/absence of amyloid pathology could increase the diagnostic accuracy or alter the course of treatment.

Regarding the typical age for undergoing amyloid PET, the respondents commonly performed scans for patients aged ≥60 to <70 years (90.4%, 47/52) or ≥50 to <60 years (80.8%, 42/52); scans for patients aged <50 years were performed by around one-third of specialists (34.6%, 18/52). Additionally, 32.7% and 11.5% of respondents performed amyloid PET scans for patients aged ≥70 to <80 years and ≥80 years, respectively, indicating that there is no age restriction for scans in South Korea.

For questions asking about the use of amyloid PET in MCI, the respondents always (9.6%, 5/52) or sometimes (75.0%, 39/52) performed scans for patients with MCI, and most of them either always (13.5%, 7/52) or sometimes (73.1%, 38/52) scanned MCI patients aged <65 years. The respondents always (26.9%, 14/52) or sometimes (57.7%, 30/52) scanned patients with MCI of unknown cause but who showed rapid deterioration. Amyloid PET was performed when the cognitive decline had progressed rapidly in MCI patients by 84.6% of respondents (26.9% always and 57.7% sometimes). Additionally, 70.2% of respondents reported that they performed scans after a monitoring period of from >6 to <18 months in patients demonstrating rapid progression. Scans were always (38.5%, 20/52) or sometimes (46.2%, 24/52) performed for MCI patients in whom the presence or absence of amyloid could alter the course of the treatment. Fifty-two of the respondents indicated that they performed amyloid PET widely in patients with MCI, especially for patients aged <65 years (13.5% always and 73.1% occasionally) and when MCI due to AD was suspected (19.2% always and 61.5% occasionally). Amyloid PET was used frequently for potentially altering the course of treatment in MCI patients, such as for differentiating cognitive decline due to depression, the effects of drugs, or for diseases such as uncontrolled diabetes (32.7% always and 42.3% occasionally), and was sometimes used when mixed pathology was suspected (55.8% occasionally and 25.0% rarely).

In response to questions about the use of amyloid PET in suspected typical AD dementia, it was reported that scans were also not uncommonly used (5.8% always, 30.8% occasionally, and 38.5% rarely), especially for patients under 65 years (30.1% always and 51.9% occasionally). Additionally, when asked about the use of amyloid PET for differential diagnosis, respondents indicated its use: for suspected focal syndromes such as primary progressive aphasia or corticobasal syndrome (21.3% always and 42.3% occasionally); and for suspected comorbid conditions such as drugs or other medical conditions (32.7% always and 42.3% occasionally); and for suspected mixed pathology with cerebrovascular diseases (11.5% always and 38.5% occasionally).

In accordance with the existing AUR "not recommended list," most South Korean specialists (n=52) never used amyloid PET for patients with a cognitive complaint that was unconfirmed by clinical examination (88.5%), nonmedical use (88.2%), patients solely with a family history of dementia (84.3%), and *APOE* ε4 carriers (51.0%); and less than half of respondents never used the technique as an alternative to genetic testing (43.1%). However, a significant number of respondents answered that they performed amyloid PET for cases of probable AD with a typical age of onset (3.9% always, 46.2% occasionally, and 36.5% rarely).

The most common reason that respondents gave for not performing an amyloid PET scan for eligible patients was patient refusal (80.8%, 42/52). Patients frequently cited expense as the main reason for refusing a PET scan (97.7%, 42/43), and some also expressed concerns about radiation exposure (41.9%, 18/43). At the time when the survey was conducted (November 2022), many respondents (71.2%, 37/52) considered that amyloid PET was not cost-effective.

The survey results combined with existing guidelines formed the basis for discussions on formulating the South Korean expert recommendations.

RECOMMENDATIONS OF DEMENTIA EXPERTS IN SOUTH KOREA

The recommendations of dementia experts in South Korea for the appropriate and inappropriate use of amyloid PET in AD are summarized in Table 2. The main premise of the South Korean expert recommendation is that, at the clinician's discretion, amyloid PET can be used for all individuals who meet the following three conditions, which are 1) cognitive complaint with objectively confirmed impairment

and 2) when knowledge of the Aβ pathology is expected to increase the diagnostic certainty and alter management, and are 3) not included on the "not recommended" list. This contrasts with the guidelines from other countries (Table 3), which provided the framework for our guidelines, and largely reflects differences related to the unique situation regarding amyloid PET in South Korea.

Previously published guidelines share some common features, but some differences are also apparent. For example, US, Italian, and Spanish recommendations restrict the use of amyloid PET to patients with suspected clinical AD and objectively confirmed cognitive impairment[44,47-49]; US, UK, Italian, and Spanish guidelines recommend amyloid PET when it could increase the diagnostic accuracy or alter management[44,46-49]; and Canadian guidelines state that amyloid PET is not currently approved for clinical practice in Canada, and so Canadian clinicians who wish to perform amyloid imaging should refer patients to a dementia center with expertise in the technique.[45] Appropriate use of amyloid PET includes patients with MCI in US, Canadian, Italian, and Spanish guidelines, with some differences in eligibility criteria[44,45,47-49]; patients with possible AD in US, UK, and Italian guidelines[44,46,47]; and early age of onset dementia in US, UK, Italian, and Spanish guidelines, although the UK guidelines do not specify an age limit for early onset (this is ≤65 years in the other guidelines).[44,46-49] Inappropriate-use criteria include determining the severity of dementia,[44,46,47] patients with probable AD and the typical age at onset,[44,46,47] as an alternative to genetic testing, asymptomatic individuals solely with a family history of dementia or at-risk genotype (one or more *APOE* ε4 alleles),[44,46,47] attempting to differentiate AD from other Aβ-associated dementias,[45,48,49] and nonmedical use.[44,46,47]

A biological definition of AD was proposed by the National Institute on Aging and the Alzheimer's Association (NIA-AA) in 2018, based on biomarkers for β amyloid deposition, pathological tau, and neurodegeneration,[8] and revised biological criteria for the diagnosis and staging of AD are currently being finalized.[54] Whilst the frequent coexistence of multiple pathologies is a major diagnostic issue with dementia and most neurodegenerative diseases that makes it difficult to decide which pathology is the leading and most relevant contributor to the presenting symptoms, confirming amyloid deposition in the brain is a crucial step in unlocking further opportunities for targeted treatment interventions. Therefore, amyloid PET is an important tool for deciding the treatment option in AD.

The following sections provide an overview of the key reasons for the recommendations that are outlined in Table 2.

Appropriate use of amyloid PET

Amyloid PET must be integrated with comprehensive clinical and cognitive evaluations performed by a dementia expert to maximize the likelihood that the imaging findings will contribute to the management of a patient.[44] In previous guidelines,[44-49] the eligibility for amyloid PET in patients with objectively confirmed cognitive impairment has varied between countries (Table 3).

Table 2. South Korean expert recommendations for the use of amyloid PET to diagnose AD

- Amyloid PET is recommended for individuals who meet both of the following conditions:
  1) Cognitive complaint with objectively confirmed impairment
  2) When knowledge of the Aβ pathology is expected to increase the diagnostic certainty and alter management
- Specific situations where the use of amyloid PET is especially recommended:
  1) To confirm early symptomatic AD (MCI due to AD or mild AD dementia) enabling prescription of a DMT agent (when DMT is available)
  2) When an amyloid PET scan can increase the certainty of the differential diagnosis of AD:
     A) Persistent or progressive unexplained cognitive impairment confirmed by a comprehensive clinical evaluation
     B) Unusual clinical presentation
     C) Atypically early age of onset
     D) Presence of a comorbid condition
- Amyloid PET is recommended at the clinician's discretion in most cases, with the following exceptions ("not recommended" list):
  1) Individuals without objective cognitive test results
  2) Cognitively unimpaired individuals
  3) Asymptomatic patients with only a family history of dementia or the presence of the APOE ε4 gene variant
  4) As an alternative to genetic testing in suspected carriers of dominant autosomal gene mutations causing AD (amyloid PET cannot replace genotyping).
  5) Determination of dementia severity
  6) Moderate-to-severe stage of dementia
  7) Non-medical use (e.g., legal purposes, insurance coverage, or employment screening)

Aβ, amyloid beta; AD, Alzheimer's Disease; APOE, apolipoprotein E; DMT, disease-modifying therapy; MCI, mild cognitive impairment; PET, positron emission tomography.

Table 3. Comparative summary of guidelines on the use of amyloid PET for the diagnosis of AD

Appropriate use of recommendation	US: Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association (2013)[44]	Italy: Italian Interdisciplinary Working Group (AIMN, AIP, SINDEM) (2015)[47]	Canada: Specialized Task Force on Amyloid Imaging in Canada (2016)[45]	UK: UK Intercollegiate Standing Committee on Nuclear Medicine (2022)[46]	Spain: SEMNIM consensus (2015)[48,49]	South Korea: current recommendations (2025)
Prerequisites for amyloid PET	• Cognitive complaint with objectively confirmed impairment. • Possible AD diagnosis: diagnosis is uncertain after a comprehensive evaluation by a dementia expert. • Presence or absence of Aβ pathology is expected to increase the diagnostic certainty and alter management.	• Cognitive impairment objectively confirmed using a standardized neuropsychological battery. • Cause of cognitive impairment remains uncertain despite an extensive clinical evaluation performed by an expert in dementia and related cognitive disorders. • Presence or absence of cerebral amyloidosis could increase the diagnostic accuracy.	• Not currently approved for clinical use in Canada. When it becomes available to Canadian clinicians, it must not be considered a routine test. • Clinicians who wish to obtain amyloid imaging should refer patients to dementia centers with expertise in this technique. • To maximize the safety and effectiveness of disclosing results, we recommend adopting parts of the sequence recently developed by Harkins et al.[109] in cognitively normal older adults participating in AD prevention studies.	• Currently, there is a paucity of evidence for the impact of these tracers on clinical outcomes. • Test is only used in patients who have been fully assessed by an expert clinician and when it is considered that amyloid imaging can contribute to the diagnosis in combination with a clinical assessment and other factors.	• Patients with cognitive decline that is clinically and objectively well-characterized in whom a neurodegenerative origin is suspected after excluding other causes of dementia: the origin is uncertain despite applying complementary tests (blood analysis and structural neuroimaging). • When the information obtained from a brain PET scan could increase the diagnostic certainty and, consequently, aid in the patient's management.	• Cognitive complaint with objectively confirmed impairment. • When knowledge of the Aβ pathology is expected to increase the diagnostic certainty and alter management.
Appropriate-use criteria	• Patients with persistent or progressive unexplained MCI. • Patients satisfying core clinical criteria for possible AD because of unclear clinical presentation, either an atypical clinical course or an etiologically mixed presentation. • Patients with progressive dementia and an atypically early age of onset (usually defined as age ≤65 years).	• Subjects affected by persistent or progressive (≥6 months) MCI, defined according to NIA-AA criteria when the expert's diagnosis based on morphological and/or functional neuroimaging is still uncertain. • MCI subjects: - When clinical onset is either atypical or uncertain without a clear diagnosis, or - When the etiology may be mixed due to a concomitant cerebrovascular disease, or - When there are potentially misleading clinical conditions.	• Patients with objectively confirmed cognitive impairment in whom there is diagnostic uncertainty after a comprehensive clinical evaluation. • Knowledge of Aβ status is expected to provide a more-precise diagnosis and alter management. • Amyloid PET could be considered in MCI patients for whom the dementia expert has determined that greater certainty about the underlying pathology would alter management (e.g., knowledge of amyloid burden in an individual <65 years old with confounding circumstances such as depression or other medical disorders, and for whom safety issues at work could have major consequences).	• Use in highly selected patients with cognitive impairment where: - AD is a possible diagnosis, but this remains uncertain after a comprehensive evaluation by a dementia expert and conventional imaging workup. - Knowledge of the presence or absence of amyloid is expected to increase the diagnostic certainty and influence patient management. • May be used in this scenario where patients have:	• Patients with persistent or progressive cognitive impairment in whom a scan would increase the certainty that the etiological diagnosis does or does not correspond to AD. • Suspected AD in early symptomatic stages, including the prodromal or MCI phase. • Atypical cognitive impairment. • Early-onset cognitive impairment or progressive dementia (before the age of 65). • Diagnosis of other neurodegenerative conditions associated with dementia.	• Amyloid PET scans are generally recommended for use in most cases, with exceptions in the "not recommended" list (Table 2).

Table 3. Comparative summary of guidelines on the use of amyloid PET for the diagnosis of AD (continued)

Appropriate use of recommendation	US: Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association (2013)[44]	Italy: Italian Interdisciplinary Working Group (AIMN, AIP, SINDEM) (2015)[47]	Canada: Specialized Task Force on Amyloid Imaging in Canada (2016)[45]	UK: UK Intercollegiate Standing Committee on Nuclear Medicine (2022)[46]	Spain: SEMNIM consensus (2015)[48,49]	South Korea: current recommendations (2025)
		• Patients with a diagnosis of possible AD, defined according to NIA-AA criteria. • Patients with cognitive decline or progressive dementia and a early age at onset (≤65 years old). • Patients affected by focal syndromes (e.g., progressive aphasia, agnosia, apraxia, or corticobasal syndrome).		- Persistent or progressive unexplained memory impairment confirmed by standard medical tests, or - Unusual clinical presentation, or - Atypical early age of onset.		
Inappropriate-use criteria	• Patients with the core clinical criteria for probable AD with the typical age of onset. • To determine dementia severity. • Based solely on a positive family history of dementia or the presence of the *APOE* ε4 allele. • Patients with a cognitive complaint that is unconfirmed on clinical examination. • In lieu of genotyping for suspected autosomal mutation carriers. • In asymptomatic individuals. • Non-medical use (e.g., legal purposes, insurance coverage, or employment screening).	• Patients meeting the criteria for probable AD and with the typical age at onset, probable DLB, probable PDD, and amyloid angiopathy (given that positivity in amyloid PET does not discriminate specific pathologies). • For the definition of severity and for following up cognitive impairment. • For asymptomatic individuals, even in the presence of familial dementia and/or with one or two of the *APOE* ε4 alleles. • For patients reporting cognitive deficits not confirmed by the objective neuropsychological evaluation. • As an alternative to genetic testing in suspected carriers of dominant autosomal gene mutations causing AD. • Non-medical use (e.g., legal and insurance purposes, or screening for employment).	• Cognitively normal individuals or for the initial investigation of cognitive complaints. • Attempting to differentiate AD from other Aβ-associated dementia (e.g., DLB or cerebral amyloid angiopathy). • Attempting to differentiate between AD clinical variants (e.g., classic amnestic AD vs. posterior cortical atrophy or the logopenic variant of primary progressive aphasia). • Attempting to differentiate between the various clinical presentations associated with the frontotemporal lobar degeneration spectrum of disorders (e.g., behavioral variant FTD vs. progressive supranuclear palsy) to try to define the underlying pathology. • Staging the severity of a dementia syndrome.	• Patients aged ≥65 years who meet the standard definitions and tests for AD. • Where there is no clinical evidence of memory impairment; that is, as a screening tool. • To assess the severity of dementia. • In asymptomatic patients with a family history of dementia. • For nonmedical reasons such as pre-employment screening.		• Individuals without objective cognitive test results. • Cognitively unimpaired individuals. • Asymptomatic patients with only a family history of dementia or the presence of the APOE ε4 gene variant. • As an alternative to genetic testing in suspected carriers of dominant autosomal gene mutations causing AD (amyloid PET cannot replace genotyping). • Determination of dementia severity • Moderate to severe stage of dementia • Nonmedical use (e.g., legal purposes, insurance coverage, or employment screening)

Aβ, amyloid beta; AD, Alzheimer's disease; APOE, apolipoprotein E; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; MCI, mild cognitive impairment; NIA-AA, National Institute on Aging-Alzheimer's Association; PDD, Parkinson's disease dementia; PET, positron- emission tomography.

Amyloid PET in MCI

Amyloid imaging in patients with MCI identifies patients with underlying AD pathology.[11,14,55,56] Many amyloid-positive MCI patients convert to AD within 1−5 years, whereas such conversion occurs in almost no amyloid-negative MCI subjects.[28,57-63] The presence of both Aβ pathology and neurodegeneration biomarkers in patients with MCI can further stratify the risk of imminent conversion to dementia.[45] In addition, with the recent availability of amyloid-targeted therapy,[64,65] it is necessary to use amyloid PET to confirm whether amyloid is the target of treatment, and follow-up amyloid PET scans can be used to determine treatment effects.

Amyloid PET in AD

Subject age

Existing guidelines recommend the use of amyloid PET in dementia with a low age at onset or possible AD (Table 3).[44-49]

Amyloid PET was indicated in patients with cognitive decline who also have progressive dementia and an early age of onset (≤65 years) when the expert could still not make a definitive diagnosis after performing both morphological and functional neuroimaging.[44,48,49] Our survey results indicate that amyloid PET is used widely in South Korea for individuals of almost all ages.

Although it has been shown that age by itself and other factors, such as resilience, may be associated with amyloid deposition and cognition,[66,67] the significance of amyloid deposition is more uncertain in older individuals that at younger ages. However, since DMT based on amyloid has been approved, in the case of early symptomatic AD, we believe that it is not realistic to place an age limit on amyloid PET imaging because it is necessary to confirm whether the patient is eligible for drug use.

Probable AD with the typical age of onset

Almost all existing AUR are against administering amyloid PET to patients over 65 years of age who have the typical history and whose examination findings are suggestive of probable AD.[44-47] This recommendation was primarily due to the high cost and low accessibility of amyloid PET, coupled with the minimal benefit it offers. In particular, the likelihood of altering treatment was very low even if patients showed amyloid positivity. However, considering the increasing introduction of amyloid-based DMT drugs and the development of various other drugs based on AD pathophysiology, the need to restrict amyloid PET in patients suspected of having probable AD with the typical age of onset is diminishing. Although many of the survey respondents considered that amyloid PET was not cost-effective when the survey was conducted, the recent availability of lecanemab in South Korea has created a situation where amyloid PET can now be considered to be cost-effective; Aβ pathology must be confirmed before administering lecanemab, and amyloid PET is one of the main methods used for this confirmation. Furthermore, the cost of amyloid PET in South Korea is lower than in other countries. If the cost of amyloid PET is covered by governmental medical insurance in South Korea with the introduction of DMT, the cost-effectiveness would be expected to increase further. The survey results also indicate that amyloid PET is already being used in a substantial number of cases of suspected probable AD with the typical age of onset in South Korea (5.8% always, 30.8% occasionally, 38.5% rarely, and 25% never). For this reason, the recommendation not to use amyloid PET for suspected probable AD with the typical age of onset could be inappropriate.

Amyloid PET for differential diagnosis

Atypical AD

In cases of probable AD with typical age of onset, the usefulness of amyloid PET imaging may be lowered in terms of clinical the usefulness of amyloid PET imaging may be lowered in clinical judgment, but it may be helpful in cases with an atypical presentation or early age of onset dementia.[45]

Atypical AD syndromes include progressive aphasia, posterior cortical atrophy, corticobasal syndrome, and frontal variant of AD (behavioral/dysexecutive syndrome),[68] and may mimic the symptoms of these proteinopathies (primary tauopathies, TDP-43 [TAR DNA-binding protein 43] proteinopathies, or synucleinopathies).[69] Misdiagnosis rates are high (up to 30%) in complex atypical patients with an uncertain diagnosis.[70]

Accurate diagnosis of atypical AD syndromes is important for individuals, especially those who are often aged <65 years and still active in the workforce.

Acurate diagnosis helps in direct therapy (i.e., to avoid unnecessary or undesired cholinesterase inhibitors or memantine prescriptions), determining a better care plan (that considers patient safety and minimizes the risk of preventable complications), and enabling patients to participate in legal and financial planning.[45]

Amyloid imaging has been shown to be useful for the differential diagnosis of atypical patients with an uncertain diagnosis,[70-84] particularly in those with a early age of onset.[85] Therefore, one of the aims of the current expert recommendation is to increase the diagnostic certainty for patients with established dementia, for whom there is substantial uncertainty as to whether the dementia is secondary to AD pathology, due to the presence of an atypical presentation or un-

usual clinical course (e.g., non-amnestic, sudden onset, and rapidly progressive), or comorbid conditions (cerebrovascular disease, other neurological disease, other medical condition, depression, or medication use) that can also cause cognitive impairment. Since atypical AD syndromes often have CSF (cerebral spinal fluid) profiles that are less clear-cut than for typical AD, amyloid PET is particularly useful biomarker in such cases.[86]

According to the survey, 63.6% of respondents indicated that they always or occasionally perform an amyloid PET scan to differentiate atypical AD or focal syndrome variants of AD. Furthermore, it was found that, in cases of individuals under the age of 65 years, 30.8% always and 51.9% occasionally perform an amyloid PET scan. It can also be helpful in patients in whom diagnosis of AD may be difficult due to various co-existing comorbidities that affect cognition.[87-90]

In the survey, 74.9% of respondents stated that they perform amyloid PET when the presence or absence of amyloid pathology is likely to alter treatment in cases of cognitive impairment due to comorbid conditions, such as depression, the influence of medication, or other inadequately controlled internal medical diseases such as diabetes or other endocrine diseases.

Differential diagnosis for other neurodegenerative diseases

Amyloid PET is generally recommended for patients with possible AD with an atypical presentation in US, UK, and Italian guidelines.[44,46,47] However, the Canadian version advises against using amyloid PET for differentiating other Aβ-associated dementias, such as dementia with Lewy bodies (DLB), or the various clinical presentations associated with frontotemporal lobar degeneration (FTLD).[45] From the perspective of therapeutic choice, it is important to distinguish atypical AD from FTLD, since medications such as acetylcholinesterase inhibitors used in AD are ineffective in FTLD.[68,91,92] Aβ plaques are generally not present in the FTLD pathological spectrum, with low rates of positive amyloid scans (0%–15%) in FTLD.[93]

However, since the rate of amyloid pathology in DLB is high, amyloid PET might not be helpful in distinguishing between AD and DLB. A recent cross-sectional study used PET to assess the Aβ load in 162 patients throughout the DLB continuum relative to 100 age- and sex-matched cognitively unimpaired (CU) individuals.[94] The DLB group included the highest proportion of Aβ-positive patients (60%), followed by MCI with Lewy bodies (41%), isolated REM sleep behavior disorder (25%), and CU (19%).[94] Additionally, DLB often presents with symptoms that are clinically distinct from AD, and can be clinically differentiated based on the diagnostic criteria for DLB proposed by McKeith et al.,[95] which include core and supportive clinical features and indicative/supportive biomarkers.[95,96] Therefore, amyloid PET is not generally helpful for differentiating AD in DLB patients. However, DLB is often clinically similar to AD, which can make it difficult to distinguish the two conditions. Moreover, DLB typically progresses more rapidly than AD, and research indicates that the prognosis is worse when DLB is accompanied by amyloid pathology. For these reasons, amyloid PET is used relatively frequently in South Korea for patients suspected of having DLB. In our survey, 50.1% of respondents stated that they always or occasionally perform amyloid PET scans in cases of suspected DLB. Therefore, the use of amyloid PET in DLB is not stated as being inappropriate in the South Korean guidelines, instead being left to the discretion of the clinician.

Amyloid PET for anti-amyloid therapy

The development of anti-amyloid therapy and DMT has important implications for the management of AD.[97] This makes it important to confirm the diagnosis of AD in order to use anti-amyloid therapies and/or DMTs that will be developed in the future. In a pivotal phase 3 trial, lecanemab made remarkable decreasing amyloid burden in early symptomatic AD and, compared with placebo, resulted in less decline on measures of cognition and function at 18 months relative to placebo.[98] Another phase 3 clinical trial using donanemab was also successful, increasing expectations for amyloid-based monoclonal antibody drug therapy.[99] Additionally, DMTs targeting various mechanisms such as pathological tau and inflammation are under development.[100,101] A diagnosis of AD confirmed by amyloid pathology is essential for using these drugs. This is particularly important in cases where possible or atypical AD is suspected. Knowledge of the presence or absence of Aβ pathology is expected to increase the diagnostic certainty and influence treatment management. For example, some South Korean patients with symptoms indicative of frontotemporal dementia inquire about anti-amyloid therapy. The use of amyloid PET in these patients can confirm the diagnosis and prevent the unnecessary administration of this treatment.

Expert recommendations for the appropriate use of amyloid PET in South Korea

- Amyloid PET is recommended for individuals who satisfy both of the following conditions (Table 2):

  1) Cognitive complaint with objectively confirmed impairment.

  2) When knowledge of the Aβ pathology is expected to increase the diagnostic certainty and alter management.

- Specific situations where the use of amyloid PET is espe-

cially recommended:

1) To confirm early symptomatic AD (MCI due to AD or mild AD dementia) enabling prescription of a DMT agent (when DMT is available).

2) When an amyloid PET scan can increase the certainty of the differential diagnosis of AD:

A) Persistent or progressive unexplained cognitive impairment confirmed by a comprehensive clinical evaluation.

B) Unusual clinical presentation.

C) Atypically early age of onset.

D) Presence of a comorbid condition.

• Amyloid PET scans are recommended at the clinician's discretion in most cases, if those are not included on the "not recommended" list

Conditions in which an amyloid PET scan is not recommended ("not recommended" list)

Without objective cognitive test results

There is currently insufficient evidence for amyloid PET assisting in the prognosis—or relieve the concerns—of individuals with a cognitive complaint but no confirmed impairment in a clinical examination. Indeed, the possibility of future AD dementia cannot be excluded on the basis of a negative amyloid PET scan, and moreover a positive amyloid PET does not necessarily mean that AD is present.[44]

CU, asymptomatic, or SCD individuals

Increasing age and the presence of the *APOE* ε4 variant are the main predictors of amyloid PET positivity in cognitively normal individuals.[102,103] It has been reported that amyloid deposition is associated with very subtle cognitive decline in individuals without dementia or MCI,[11,14,55] especially among *APOE* ε4 carriers.[104] However, from a diagnostic standpoint, there is insufficient research evidence for amyloid-positive CU subjects progressing to AD.[105] Consequently, in CU individuals, the mere presence of amyloid positivity alone is inadequate for an AD diagnosis.[45] However, a combination of abnormal amyloid and tau PET examinations is strongly associated with short-term cognitive decline in CU individuals, and therefore is of clinical relevance.[106]

For individuals with SCD, therefore, a cognitive complaint that is unconfirmed on clinical examination, there is insufficient evidence to suggest that amyloid PET can aid prognostic judgments or relieve the concerns of such individuals. For asymptomatic individuals, there is significant potential for patients/families to make inaccurate assumptions about the risk and future outcomes on the basis of amyloid PET results.[44] Furthermore, as there is no evidence yet of the effective use of amyloid-based monoclonal antibodies in CU individuals, amyloid PET is not recommended for this group.[45]

Asymptomatic patients with only a family history of dementia or the presence of the APOE ε4 gene variant

There is no evidence that amyloid PET performed solely based on the family history or the *APOE* genotype aids the prognosis or course of cognitive impairment.

As an alternative to genetic testing in suspected carriers of dominant autosomal gene mutations causing AD

While autosomal dominant AD will result in future AD dementia, a positive amyloid PET scan does not confirm the future development of AD dementia in suspected carriers. Consequently, in suspected carriers of dominant autosomal gene mutations causing AD, amyloid PET cannot replace genetic testing.[44]

Dementia severity

The use of amyloid imaging to determine the severity of any cognitive disorder is not supported by the available data. The current evidence overwhelming supports that there is no correlation between the Aβ burden measured with amyloid PET and the severity of cognitive deficits in patients with dementia.[93] A recent study indicated that fluorodeoxyglucose (FDG) PET, which measures the brain's glucose consumption as a marker of neural activity, may be better than amyloid PET for assessing the progression and severity of AD and MCI, since the latter is unable to differentiate between individuals with very mild and very severe symptoms.[107]

Nonmedical use

There is no evidence to support the nonmedical use of amyloid PET beyond evaluating amyloid deposition to diagnose AD. Specifically, there is no evidence to support the use of amyloid imaging to inform physicians when they are consulted on legal-, disability-, and employment-related issues, including competency assessments, insurability screening, or assessing employability or the ability to perform daily activities (e.g., driving, piloting an aircraft, or making financial decisions).[44]

CONCLUSIONS

In conclusion, the evolving field of AD diagnostics warrants a reconsideration of previous AUR that aimed to restrict the utilization of amyloid PET. The recognition that AD exists across various stages—from asymptomatic to severe dementia—challenges the traditional paradigm equating AD with dementia. Of course, a positive result in amyloid PET does not guarantee the immediate progression to dementia. How-

ever, individuals with amyloid positivity—even in the CU state with abnormal amyloid and tau co-pathologies—may have a higher risk of future cognitive decline.[106] Amyloid PET for CU is currently included in the "not recommended" list, but this is because there is no appropriate treatment supported by evidence even if amyloid pathology is confirmed at that point. However, it is quite possible that the amyloid PET recommendation will change if drugs for preclinical AD are developed in the future.

Whilst acknowledging that a major diagnostic issue with dementia (and indeed most neurodegenerative diseases) is the frequent coexistence of multiple pathologies, with it being difficult to decide which one is the leading and most relevant for symptom development, confirming amyloid deposition in the brain is crucial to unlocking further opportunities for targeted treatment interventions. In addition to focusing on clinical symptoms and the results from other diagnostic tests, including the future use of high-performance blood tests that are being developed for the evaluation of cerebral amyloid pathologies,[108] amyloid PET remains an important and reliable in vivo tool for detecting the amyloid burden in AD. Furthermore, the impact of DMT for MCI and early AD on amyloid PET usage is evident. Almost all (96.0%) of 59 South Korean physicians specializing in dementia expressed their readiness to perform amyloid PET in clinically early symptomatic AD cases if DMT drugs were available.

Therefore, given the unique situation and already widespread use of amyloid PET in South Korea, it is recommended to perform amyloid PET at the clinician's discretion when patients fulfill the necessary preconditions and are not included in the "not recommended" list.

Supplementary Materials

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Availability of Data and Material

All data generated or analyzed during the study are included in this published article (and its supplementary information files).

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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