2024 AUC for Amyloid and Tau PET

Updated Appropriate Use Criteria for Amyloid and Tau PET in Alzheimer's Disease

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Abstract:
INTRODUCTION
The Alzheimer's Association and Society of Nuclear Medicine and Molecular Imaging convened a multidisciplinary Workgroup to update Appropriate Use Criteria for amyloid Positron Emission Tomography (PET) and develop AUC for tau PET.
METHODS
The Workgroup identified key research questions that guided a systematic literature review on clinical amyloid/tau PET. Building on this review, the Workgroup developed 17 clinical scenarios in which amyloid or tau PET may be considered. A modified Delphi approach was used to rate

each scenario by consensus as “rarely appropriate,” “uncertain” or “appropriate”. Ratings were performed separately for amyloid and tau PET as stand-alone modalities.

RESULTS

For amyloid PET, 7 scenarios were rated “appropriate”, 2 “uncertain” and 8 “rarely appropriate”. Ratings for tau PET were: 5 scenarios “appropriate”, 6 “uncertain” and 6 “rarely appropriate.”

DISCUSSION

AUC for amyloid and tau PET provide expert recommendations for clinical use of these technologies in the evolving landscape of Alzheimer’s disease diagnostics and therapeutics.

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1. Introduction and Scope

Alzheimer's disease (AD) is defined neuropathologically by the deposition of extracellular plaques composed of aggregated forms of the Amyloid-β (Aβ) polypeptide, and intra-neuronal neurofibrillary tangles composed of aggregated hyper-phosphorylated tau protein.[1] In the past twenty years, positron emission tomography (PET) radiotracers were developed to image amyloid plaques and tau tangles *in vivo*[2-7]. Currently, three fluorine-18 labelled amyloid radiotracers (^{18}F-florbetapir, ^{18}F-flutemetamol, ^{18}F-florbetaben) are approved for clinical use by regulatory agencies in the U.S. and other countries to estimate amyloid plaque density in adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive decline. In 2020 the United States (U.S.) Food and Drug Administration (FDA) approved the tau radiotracer ^{18}F-flortaucipir to estimate the density and distribution of neurofibrillary tangles (NFTs) in adult patients with cognitive impairment who are being evaluated for AD.

In 2013, a taskforce convened by the Alzheimer's Association (AA) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) developed Appropriate Use Criteria (AUC) to define the types of patients and clinical circumstances in which amyloid PET could be used, and, importantly, clinical scenarios in which amyloid PET was felt to be inappropriate[8]. The goal of this article is to update the AUC for amyloid PET based on additional data that have emerged in the decade since the original AUC were published, including advances in therapeutics designed to lower cerebral amyloid burden. Recognizing these important advances, in October 2023 the U.S. Centers for Medicare and Medicaid Services (CMS) retired its 2013 National Coverage Decision which restricted coverage of amyloid PET to a single scan per patient under approved research studies, thus promoting greater patient access to this important clinical tool. CMS did not issue a non-coverage policy for tau PET; thus, it is covered by CMS under the discretion of the local Medicare Administrator Contractors. Additionally, we propose for the first time AUC for tau PET, recognizing that this is a relatively novel technology and that data on its clinical utility are currently limited. The revised AUC were developed by a multidisciplinary Workgroup of experts convened by AA-SNMMI (see Methods).

The primary goal of these updated AUC is to assist clinicians in identifying clinical scenarios in which amyloid or tau PET may be useful for guiding the diagnosis and management of patients who have, or are at risk for, cognitive decline, while also highlighting scenarios in which PET scans are unlikely to provide clinically useful information. The primary intended audience is dementia specialists who spend a significant proportion of their clinical effort caring for patients with cognitive complaints. The manuscript is also meant to serve as a general reference for a broader audience interested in implementation of amyloid and tau PET in clinical practice. In addition, the AUC are intended to support policy makers and payers in promoting cost-effective access to this important diagnostic tool to patients who are most likely to benefit in the setting of limited healthcare resources. Finally, the Workgroup members recognize that amyloid and tau PET are part of a growing landscape of molecular biomarkers of AD pathophysiology, including cerebrospinal fluid (CSF) and blood-based biomarkers of amyloid, tau, and neurodegeneration. The reader is referred to published AUC for CSF biomarker[9] and Appropriate Use Recommendations for blood-based AD biomarkers[10]. The optimal integration of the entire armamentarium of AD biomarkers into future diagnostic and care algorithms is beyond the scope of this article but represents an important area for future research.

2. Background

The current document is an update the previously published AUC for amyloid PET[8]. The update integrates extensive literature published over the past decade examining the diagnostic and prognostic value of amyloid PET in longitudinal clinical cohorts and observational studies; evaluating the clinical utility of amyloid PET for patient diagnosis, management and health outcomes; further validating the diagnostic validity of amyloid PET in prospective PET-to-autopsy studies; and employing amyloid PET in AD clinical trials, including the development of amyloid-targeting antibodies which recently received approval from the U.S. FDA for the treatment of early clinical stages of AD[11-13].The updated AUC reflect an increasing awareness that amyloid deposition begins two decades or longer before the onset of cognitive impairment, defining a prolonged preclinical phase of AD, with potential increased demand for testing among cognitively unimpaired individuals or individuals experiencing subjective cognitive decline (see definitions below). Finally, the updated AUC examine for the first time the potential role of tau PET in common clinical scenarios given recent FDA approval of ^{18}F-flortaucipir for clinical use. Importantly, neocortical tau PET signal appears more proximally to clinical symptoms than neocortical amyloid PET signal. In contrast to the much more extensive literature on amyloid PET, ^{18}F-flortaucipir is a relatively new radiopharmaceutical with limited data, particularly as pertaining to longitudinal follow-Up and clinical utility. As with amyloid imaging, recommendations represent expert opinion based on currently available information.

Amyloid and tau PET detect amyloid plaques and neurofibrillary tangles, the core elements that collectively define AD neuropathology. In the clinical setting, their primary role is to provide evidence for or against the presence of these disease-defining lesions in patients who are seeking assessment for cognitive symptoms. The PET scans should be performed when there is significant uncertainty regarding the etiology of cognitive impairment after a comprehensive assessment by a dementia specialist (see definition below), AD is a diagnostic consideration, and knowledge of amyloid or tau status is expected to help establish an etiologic diagnosis and guide patient management (e.g., to confirm the presence of amyloid plaques in a patient who is a candidate for an amyloid lowering therapy). Amyloid or tau PET should not be used as a substitute for a comprehensive clinical examination, which should include a detailed medical and neurobehavioral history, physical examination, mental status testing, blood tests to rule-out potentially reversible causes of cognitive impairment and structural brain imaging. The entirety of these clinical data are required to optimally integrate amyloid/tau PET results into clinical decision-making regarding diagnosis and patient management.

The guidelines presented here highlight general principles for integrating amyloid and tau PET into clinical care, including the potential appropriateness of testing in specific clinical scenarios. These represent general recommendations and should not be considered a substitute for clinical judgment exercised by the healthcare provider caring for an individual patient.

As recommended in the previous AUC, the following sequence of events would generally be appropriate for the integration of amyloid or tau PET into clinical practice: (i) evaluation by a dementia expert to assess the need for diagnostic testing, possibly to include amyloid or tau PET, if the AUC are met; (ii) referral to a qualified provider of PET services; (iii) performance, interpretation, and reporting of the PET result according to established standards; (iv) incorporation of the PET result into the clinical assessment process by the dementia expert; and (v) disclosure of the PET result by the dementia expert to the patient, family and care partners, along with discussion of the result and its management consequences.

3. Key Definitions

The following definitions provide clarification of key terms used in this document and the clinical scenarios for appropriate use presented by this workgroup.

The Continuum of Cognitively Unimpaired, Subjective Cognitive Decline, Mild Cognitive Impairment and Dementia

Cognitive impairment acquired in adulthood is diagnosed by a history from the patient and a knowledgeable proxy for the patient, and by examination of objective cognitive performance under direct observation by a skilled clinician. Cognitive functioning exists on a continuum anchored at one end by the state of being cognitively unimpaired and, on the other end, by the state of severe dementia, with intermediate states in between. The definitions of cognitive impairment to be used in the current document are grounded in the clinical judgment that they represent a decline from a prior higher level of functioning. More detailed definitions are found in the NIA-AA Research Framework consensus definitions (Table 5 in[14], but below are definitions used by this workgroup to establish AUC for amyloid and tau PET.

- **Cognitively unimpaired (CU):** Cognitive performance is within the expected range for that individual based on clinical judgment or cognitive test performance, and the patient does not endorse significant cognitive complaints[14].
- **Subjective cognitive decline (SCD):** Cognitive complaints in the absence of objective evidence of decline below expected normative levels[15].
- **Mild cognitive impairment (MCI):** Cognitive performance in at least one domain that is below the expected range for that individual based on all available information, but daily activities are performed in a largely independent manner. The definition of MCI allows for mild functional impact on the more complex activities of daily life[14,16].
- **Dementia:** Substantial cognitive impairment that affects multiple cognitive domains, interferes with daily functioning and results in loss of independence. Dementia can be further subdivided into mild, moderate and severe stages reflecting incrementally worse functioning in first instrumental (i.e., complex) and then basic activities of daily living[14,17].

Clinical diagnosis requires the use of categorical syndromic diagnostic labels such as SCD, MCI or dementia, but there are many patients whose clinical presentation falls in between two of these. Thus, while this document will make recommendations that are syndrome-specific, clinical judgment requires that each patient must be understood as unique and not as a generic exemplar of a categorical diagnosis.

Alzheimer's Disease and the Etiology of cognitive disorders

In the context of the current document, where amyloid and tau biomarkers are being applied to patients with cognitive impairment, we maintain a conceptual separation between cognitive disorders and underlying etiology. The most common symptomatic presentation of AD pathology is a disorder that begins with amnestic complaints that may not substantially interfere with daily activities, and then progresses to a multidomain cognitive disorder (i.e., variably involving language, visuospatial and executive deficits as well as behavioral abnormalities)[16,17]. The clinical syndrome of amnestic dementia, originally referred to as probable AD in the 1984 NINCDS-ADRDA criteria,[18] is often, but not always, due to AD pathology. Neuropathologic

investigations[19] have shown that clinical diagnostic criteria alone have suboptimal accuracy for AD as defined pathologically. Moreover, several non-amnestic cognitive presentations that are more common in younger patients, such as visual, language, or behavioral/dysexecutive variants, were shown to be due to AD neuropathology[20]. The lack of a close clinical-pathological relationship between clinical presentation and neuropathology (or biomarker) evidence for AD, requires us to recognize the pleomorphic clinical presentations of AD pathology, and, that in the setting of historically typical amnestic cognitive disorders, alternative brain pathologies could be relevant.

Cognitive Disorder of Uncertain Etiology

We will define "cognitive disorder of uncertain etiology" in this document (which is explicitly AD-centric) when there are simultaneously features that are typical for AD pathology and features that are typical for non-AD pathology. In the 1984 NINCDS-ADRDA criteria,[18] this pattern of features that did not exclude AD but were not specific for AD was assigned a diagnosis of "possible AD." In the prior amyloid PET ,[8] such symptom complexes were labeled as "unexplained." Advances in neuropathology and antemortem biomarker investigations have shed new light on this common situation. First, many clinical features – whether cognitive symptoms, non-cognitive symptoms, temporal profile, associated medical diagnoses, structural imaging features – are not as specific for one diagnosis as previously believed. Further, multi-etiology cognitive disorders are more common than single etiology disorders[21], so that striving to apply one and only one etiological diagnosis is conceptually naïve. While such a group of possible AD and unexplained MCI or dementia represents a very heterogeneous group, it is an important group for the current discussion of AUC for amyloid and tau PET.

Dementia Expert

The appropriate integration of amyloid and tau PET into the assessment of cognitive decline requires clinical expertise and experience in the evaluation of dementia. Consistent with previous AUC[8,22], we define a "Dementia Expert" as a physician typically trained and board-certified in neurology, psychiatry, or geriatric medicine who devotes a substantial proportion (at least 25%) of patient contact time to the evaluation and care of adults with acquired cognitive impairment or dementia. Physicians can self-identify as a Dementia Expert based on their training, knowledge base and clinical experience. Importantly, not all neurologists, psychiatrists or geriatricians are Dementia Experts, and conversely clinicians trained in other disciplines may possess the requisite expertise in dementia care. The guiding principles are that Dementia Experts should be: (1) skilled at evaluating, diagnosing and staging a broad spectrum of cognitive disorders; (2) familiar with the techniques of amyloid and tau PET (including their strengths and limitations); (3) able to interpret the meaning of amyloid and tau PET results in the broader clinical context of individual patients; and (4) able to communicate PET results and their implications for diagnosis and care to patients and families in a safe and effective manner, employing best practices for disclosure.

4. Amyloid PET and Tau PET Technology, Radiotracers, and Interpretation

This section complements and updates information provided in the 2013 publication on the AUC for Amyloid PET[8,22]. PET is an established molecular imaging technique that is used to detect, measure, and map molecular targets in the living human, including the *in vivo* localization of aggregated proteins, such as amyloid plaques and tau neurofibrillary tangles. This is possible because PET can measure the *in vivo* distribution of radioactive positron-emitting imaging agents, or radiopharmaceuticals, that bind selectively and specifically to the protein target. The high sensitivity of PET enables measurement of picomolar *in vivo* concentrations, after intravenous administration of trace amounts of the radiopharmaceutical (or radioligand). In studies of neurodegeneration, carbon-11 and fluorine-18 are the positron-emitting radionuclides that are most often incorporated into pharmaceuticals, yielding radiopharmaceuticals with radioactive half-lives of about 20 minutes and 110 minutes, respectively. The longer half-life of fluorine-18 enables widespread distribution and use of these radiopharmaceuticals beyond the manufacturing site.

Carbon-11 Pittsburgh Compound-B (PiB) is a well-established radiopharmaceutical[23] that is widely used by research groups that can produce it on site. PiB often serves as a reference standard to which other amyloid PET agents are compared. Three fluorine-18 Aβ agents are approved by the U.S. Food and Drug Administration, European Medicines Agency, and other global regulatory agencies for clinical use "to estimate amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive decline": ^{18}F-florbetapir (commercial name Amyvid™), ^{18}F-florbetaben (Neuraceq™), and ^{18}F-flutemetamol (Vizamyl™). A fourth fluorine-18 labelled agent that compares most closely to PiB in terms of tissue contrast is ^{18}F-flutafuranol (formerly NAV4694). However, this radiopharmaceutical is not currently approved for clinical use in the U.S. or Europe. Figure 1 illustrates the chemical structures of the above-listed amyloid tracers and of the tau tracer ^{18}F-flortaucipir (Tauvid™)[7,24-27]. The reader is referred to the SNMMI Procedure Standard/EANM Practice Guideline for Amyloid PET Imaging of the Brain[28] for more information of how to perform an amyloid PET scan.

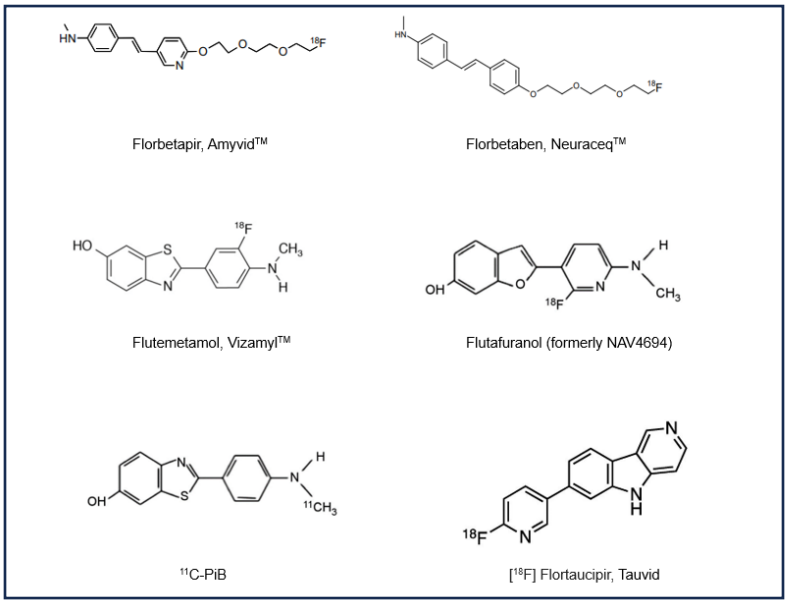

Figure 1. Chemical structures of amyloid and tau radiotracers

The clinical interpretation of Amyloid PET scans is based primarily on visual interpretation methods approved by regulatory agencies following validation in PET-to-autopsy studies performed in end-of-life populations. In patients with absent-to-low density of amyloid plaque deposition, PET scans show only non-specific tracer retention in white matter. In patients with moderate-to-high density of amyloid plaques, tracer retention extends into neocortex (Figure 2). Earliest amyloid PET signal is often seen in posterior cingulate cortex, precuneus and frontal regions[29], while widespread neocortical uptake is common by the time patients develop cognitive impairment. Each of the three FDA-approved amyloid radiotracers is visualized in different gray/white or color scales (Figure 2), and the specific criteria for scan positivity (including the specific regions investigated) differ slightly across the three agents.

Table 1.

Amyloid Agent	Image Display	Number of Regions for Positive Scan
Florbetapir F 18 370 MBq (10 mCi)	**Color Scale**: Gray scale or inverse gray scale **Regions:** temporal, parietal (including precuneus), frontal, and occipital	Two, or only one if gray matter uptake exceeds white matter uptake.
Flutemetamol F 18 185 MBq (5 mCi)	**Color scale:** Rainbow or Sokoloff. Adjust the color scale to set the pons to approximately 90% maximum intensity. **Regions:** temporal, parietal, posterior cingulate/precuneus, frontal, striatum	One
Florbetaben F 18 300 MBq (8.1 mCi)	**Color scale:** gray scale or inverse gray scale. **Regions**: temporal, parietal, posterior cingulate/precuneus, and frontal	One
Tau Agent		
Flortaucipir F 18 370 MBq (10 mCi)	**Color Scale:** color scale with a rapid transition between two distinct colors and adjust the scale so that the transition occurs at the 1.65-fold threshold. Neocortical activity in either hemisphere contributes to image interpretation.	A positive scan shows increased neocortical activity in posterolateral temporal (PLT), occipital, or parietal/precuneus region(s), with or without frontal activity. Neocortical activity in either hemisphere can contribute to identification of the positive pattern[30,31].

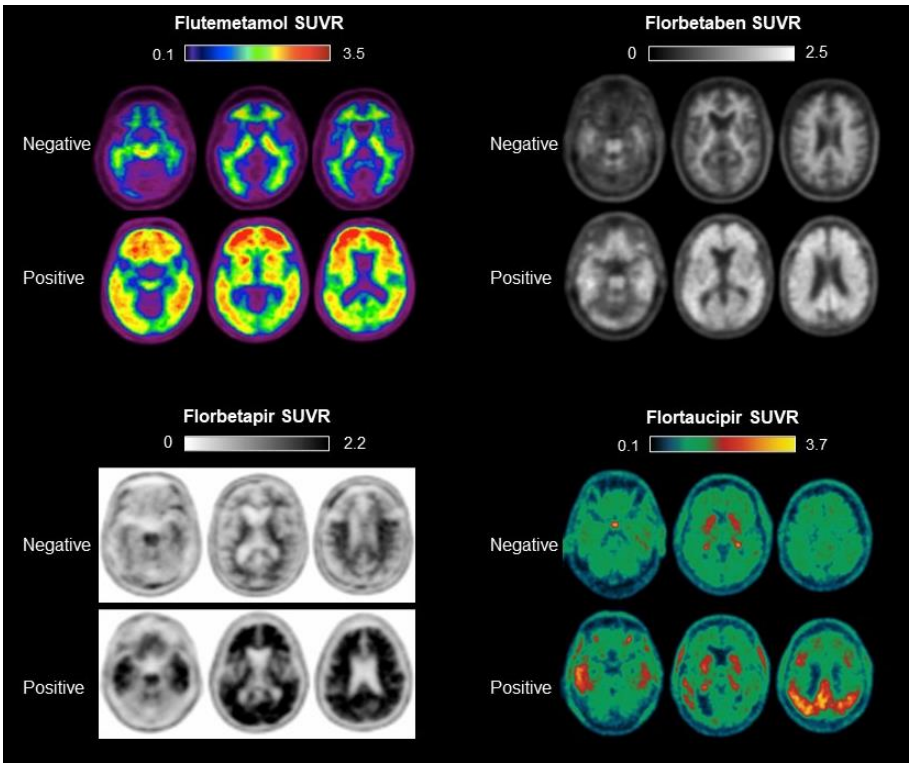

Figure 2. Examples of positive and negative Aβ and tau PET scans with FDA approved radiotracers. SUVR images were created using pons (^{18}F-flutemetamol) whole cerebellum (^{18}F-florbetaben, ^{18}F-florbetapir) and inferior cerebellar gray matter (^{18}F-flortaucipir) as reference regions.
Each image is displayed in the approved gray/white or color scale for clinical interpretation.

Quantification of amyloid PET is often performed in research studies and clinical trials. The most common quantitative measure is the standardized uptake value ratio (SUVR) which is the ratio of radiopharmaceutical uptake in a target region (e.g., neocortical regions that are known to accumulate amyloid plaques) divided by uptake in a nonspecific reference region that is relatively spared of pathology (e.g., cerebellum), measured at a time after injection when these ratios were shown to be stable (varies by radiotracer). The “Centiloid” scale can be used to standardize and compare amyloid PET quantification across radiotracers and image processing methods. In this scale, 0 Centiloids (CL) represents the average neocortical uptake in young cognitively unimpaired individuals who are very unlikely to have amyloid deposition, while 100 CL represents the mean uptake in patients with mild-moderate dementia due to AD. Thresholds for scan positivity typically vary between 10-40 CL units, with lower thresholds increasing the sensitivity to detect early pathology.[32-34]Standardized imaging acquisition and processing is established for amyloid PET, and several commercial software packages that can be used to derive SUVR and CL outcomes were developed to assist with scan interpretation in clinical practice, though use of quantification is not currently included in the FDA labels.[35] Future clinical use of amyloid PET quantification may be particularly important for objectively gauging longitudinal changes in amyloid burden in individual patients, e.g., to measure clinical response to an amyloid lowering therapy (see Clinical Scenario 15).

Tau PET is currently performed using F-18 radiopharmaceuticals. ^{18}F-Flortaucipir (FTP, commercial name: Tauvid™) was the first widely used tau agent, and in 2020 was granted FDA

approval “to estimate the density and distribution of aggregated tau NFTs for adult patients with cognitive impairment who are being evaluated for Alzheimer’s disease[36].”
Several additional tau-selective radiotracers were subsequently developed, including ^{18}F-MK-6240, ^{18}F-RO69558948, ^{18}F-GTP-1, ^{18}F-PI-2620 and ^{18}F-PM-PBB3 (also known as ^{18}F-APN-1607), although none have yet received FDA approval. All tau tracers were developed based on their ability to bind to AD-related neurofibrillary tangles. Most show absent-to-weak binding to non-AD tauopathies (e.g., progressive supranuclear palsy, corticobasal degeneration, chronic traumatic encephalopathy, molecular sub-types of frontotemporal dementia), though ^{18}F-PI-2620 and ^{18}F-PM-PBB3 are currently being evaluated as broader spectrum tau imaging agents. Notably, ^{18}F-PI2620 received orphan drug indication as a biomarker for tau deposition in 4-repeat tauopathies (i.e., PSP and CBD). All tau tracers exhibit varying degrees and patterns of “off-target” binding (i.e., binding to non-tau targets), typically in basal ganglia, meninges, choroid plexus, and midbrain nuclei (substantia nigra and red nucleus).

As with amyloid tracers, clinical interpretation of FTP tau PET scans is based on visual interpretation (Figure 2). A scan is interpreted as “negative AD tau pattern” if there is no neocortical tracer uptake, or if uptake is limited to the medial temporal, anterolateral temporal, or frontal cortex. A positive “AD pattern” is defined by extension of tracer retention into the posterolateral temporal or occipital cortex, with further extension into parietal cortex, posterior cingulate/precuneus cortex and frontal cortex seen in more advanced disease (Figure 2)[36]. In research studies, SUVR values are calculated to quantify tau PET uptake across radiotracers in various target regions of interest, with earliest signal typically detectable in entorhinal cortex and other medial temporal structures, followed by spread into inferior temporal gyrus (the latter usually occurring in the setting of positive amyloid PET). Efforts are underway to develop standardized quantitative tau PET scales across radiotracers and analytic approaches, analogous to the CL scale used for amyloid PET standardization[37] . Tau PET quantification may enhance sensitivity for early-stage disease (e.g., Braak Stages III/IV)[38], assist with disease staging[39], and gauge longitudinal change in tau burden as a result of disease progression or in response to therapeutic interventions[40].

Standardized acquisition of the PET scans, following FDA labels, is necessary for reproducible results. High-quality training of readers is essential to ensure consistently accurate interpretation of amyloid and tau PET. As with all nuclear medicine imaging, readers also need to learn to recognize important technical or patient-related artifacts[35].

5. Neuropathologic Target of Amyloid and Tau PET Ligands

At autopsy, amyloid plaques are visualized using thioflavin fluorescent dyes, silver impregnation techniques, or antibody-based immunohistochemistry. Neuritic plaques are the pathognomonic plaque type in AD that are morphologically defined by incorporation of dystrophic tau-positive neurites into the amyloid deposit[41,42]. The topographic distributions of amyloid plaque deposition and neurofibrillary tangle accumulation are used to assess the level of AD neuropathologic change, as reflected by the ‘ABC’ score in the NIA-AA neuropathologic guideline[41,42]. The Amyloid component is derived from topographic distribution of any plaque type using Thal amyloid phase [43] the tau component relies upon Braak tangle stage [44,45] and given the significance of neuritic plaques an additional amyloid component is accounted for by Consortium to Establish a Registry for Alzheimer's Disease (CERAD) score[46]. The ABC score

integrates all three components to classify an individual as having “no,” “low,” “intermediate” or “high” AD neuropathologic change, with “intermediate-high” changes considered to be clinically relevant.

Neuroimaging and neuropathology studies demonstrate common spatial patterns of amyloid deposition beginning in the neocortex, then involving limbic structures and diencephalon, and lastly found in cerebellum[29,43,47-49]. The topographic distribution of amyloid plaques is similar across different clinical presentations of AD (i.e., memory, dysexecutive, language, visuospatial predominant presentations)[50-52].

In typical AD, tau accumulation is first observed in the entorhinal cortex (Braak stages I-II), followed sequentially by involvement of limbic and paralimbic structures (Braak stages III-IV), association cortices (Braak stage V), and lastly primary cortices (i.e., primary sensorimotor, visual or auditory cortices, Braak stage VI)[44,45] .Less commonly, the distribution of tangles presents instead with “hippocampal sparing” or “limbic predominant” patterns. “Hippocampal sparing AD” is defined by greater cortical involvement relative to limbic structures and is more commonly observed in patients presenting with an atypical, non-amnestic phenotype[53,54]. In direct contrast, limbic structures are greatly affected relative to cortex in “limbic predominant AD,” with the overwhelming majority of patients presenting with an amnestic phenotype. Different clinical variants of AD show distinct topographic densities of neurofibrillary tangles, with highest tangle densities found in the regions that are most clinically affected[55]. Studies with tau PET have replicated these three patterns of tau distribution *in vivo*[56].

FDA approval of amyloid and tau PET radiotracers was based on studies that compared visual interpretation of antemortem PET to the distribution of amyloid and tau aggregates at autopsy. The pivotal studies leading to regulatory approval were conducted in participants near the end of life, resulting in short (several months) intervals between PET and autopsy[57-59]. For amyloid tracers, majority visual reads of amyloid PET scans conducted with FDA-approved radiotracers were found to have 88%-98% sensitivity and 80%-95% specificity when compared to CERAD moderate-frequent neuritic plaques at autopsy. Studies that compared antemortem PET to Thal phase found scan positivity typically corresponded to Thal Phase 2-3. Thus, it is important to note that a negative scan does not equate to “no” amyloid deposition, though low levels of amyloid that are below the threshold of detection are much less likely to contribute to cognitive impairment[60]. Conversely, positive scans can be seen in patients who have diffuse amyloid plaque deposition (often seen in diffuse Lewy body disease) or cerebrovascular amyloid deposits (in cerebral amyloid angiopathy), but who do not meet neuropathologic criteria for intermediate-high AD neuropathological changes (ADNC).

In the autopsy validation study of ^{18}F-flortaucipir[36], majority visual reads of antemortem PET scans showed 92% sensitivity and 80% specificity compared to Braak stage ≥ V neurofibrillary pathology. This degree of tau neuropathology is nearly always associated with cognitive impairment and Amyloid PET positivity. Therefore, a positive visual read of ^{18}F-flortaucipir PET in isolation may be sufficient to “rule-in” a significant contribution of AD to cognitive impairment. However, when applying the visual read method described above, scans were visually read as consistent with AD in only ~20% of patients who died with Braak stage III-IV tau pathology, though this level represents the median Braak stage observed in patients who died at the MCI stage of impairment. Quantification of tau PET, particularly in medial temporal lobe, may enhance the sensitivity of the scan to earlier Braak stages[38], but this is not performed routinely in clinical practice. The limited sensitivity of ^{18}F-flortaucipir PET to early-stage disease due to

the visual read method used in the autopsy validation study may limit the clinical utility of the scan in patients with MCI or earlier clinical stages that are typically associated with less advanced tau pathology.

6. Relation of Amyloid and Tau PET to other diagnostics

6.1. Other nuclear medicine procedures

PET with the radiolabelled glucose analogue ^{18}F-fluorodeoxyglucose has been used to image regional cerebral glucose metabolism in a wide variety of neuropsychiatric diseases for over four decades. ^{18}F-fluorodeoxyglucose (FDG)-PET can be helpful in the differential diagnosis of cognitive disorders by demonstrating characteristic patterns of glucose hypometabolism that are uniquely associated with characteristic underlying neuropathologies. The most common ^{18}F-FDG pattern in AD reveals hypometabolism in temporoparietal cortex, with prominent involvement of posterior cingulate cortex and precuneus. Frontal cortex is typically spared in early clinical stages. The anatomic pattern overlaps to a large extent with cortical atrophy seen on magnetic resonance imaging (MRI), but some studies suggest that ^{18}F-FDG may be more sensitive than MRI at early disease stages, and patterns may be more apparent on qualitative reads for individual patients. [61] ^{18}F-FDG-PET has an established role in the diagnosis of frontotemporal dementia (FTD), demonstrating frontal or anterior temporal predominant hypometabolism (with sparing of posterior cortical regions) in behavioural or language variants of FTD. [61] In a head-to-head study of amyloid vs. ^{18}F-FDG-PET in over 100 autopsy-confirmed cases (primarily AD and FTD), amyloid PET had higher sensitivity than ^{18}F-FDG-PET for the presence of AD neuropathology with similar specificity, although both modalities performed similarly in determining the causative neuropathology[62]. ^{18}F-FDG-PET can also be useful in evaluating dementia with Lewy bodies (DLB) with occipital hypometabolism and preserved metabolism in the posterior cingulate ("cingulate island sign") helping to distinguish the metabolic pattern from that of AD. [63-65]Characteristic patterns have also been reported in atypical parkinsonian syndromes, such as corticobasal degeneration, progressive supranuclear palsy and multiple system atrophy[66].

Presynaptic dopaminergic imaging, (e.g., ^{123}I-DaTscan SPECT or ^{18}F-FDOPA-PET) supports the differential diagnosis between DLB and AD by demonstrating loss of dopaminergic cells in the nigrostriatal pathway, with decreased radiotracer uptake in the putamen and caudate. There is ~80% sensitivity and about 92% specificity for the diagnosis of DLB compared to neuropathologic diagnoses obtained at autopsy[61,67,68]. However, presynaptic dopaminergic denervation can be present in neurodegenerative causes of parkinsonism other than DLB.

Apart from the most commonly employed PET tracers, other PET tracers are being developed with high potential in dementia research. These include markers of neuroinflammation[69,70] and synaptic density. [71]PET radiotracers that bind to other protein aggregates associated with neurodegeneration, such as α-synuclein and TAR DNA-binding protein 43 (TDP-43), are currently in early stages of development[72-74].

6.2. Fluid biomarkers of Amyloid and tau

Different isoforms of amyloid can be reliably measured in cerebrospinal fluid, where the levels of Aβ42 are reduced by 40-60% in individuals with amyloid plaques compared with amyloid-

negative controls, while CSF Aβ40 levels do not discriminate patients with and without plaque deposition. CSF measures of total tau and phosphorylated tau (Phosphorylated tau [P-tau]; at residues 181 or 217) are elevated in patients with AD. Elevated total tau levels are not specific to AD, and are also seen in other conditions associated with neuronal injury, including stroke, traumatic brain injury and Creutzfeldt-Jakob disease. Elevated CSF P-tau181 and P-tau217 are more specific for AD, and may reflect amyloid-mediated changes in tau phosphorylation and secretion[75,76].

Numerous studies have shown a high concordance between amyloid-PET imaging and the CSF Aβ42/Aβ40 and Aβ42/P-tau181 ratios (see e.g.[77,78]). These CSF ratios perform better than measuring concentrations of Aβ42 or p-tau alone when predicting amyloid-PET status[78,79]. Across the AD continuum, CSF P-tau, especially P-tau217, is moderately associated with both the load of amyloid and tau PET[80,81]. Alternative tau assays, such as P-tau205 and (in particular) microtubule-binding region of tau at residue 243 (MTBR-tau243), may track better with neurofibrillary tangle deposition and tau PET[82], but are not yet available outside of research studies.

When using the clinically approved high precision CSF assays, the CSF Aβ42/Aβ40 (or Aβ42 /p-tau) ratio can predict the visual classification of amyloid-PET images with similar accuracy to quantitative assessments (SUVRs) of the same PET images.[78]Not surprisingly, amyloid-PET and CSF AD ratios detect early AD with similar accuracy, and there is no added value of combining the two measures to detect amyloid positivity.[83] Fully automated CSF AD biomarker assays have recently been approved by the FDA and other regulatory authorities.

In recent years there have been major advances in developing high precision plasma assays for AD biomarkers[84]. Mass spectrometry-based methods for quantification of Aβ42/Aβ40 in plasma have shown high correlation with CSF Amyloid biomarkers or amyloid-PET.[85,86] However, the levels of plasma Aβ42/Aβ40 are decreased by only 8-15% in individuals with cerebral Amyloid pathology, compared to the 40%-60% decreases seen in CSF. Therefore, the robustness of plasma Aβ42/Aβ40 at the individual patient level may be suboptimal for clinical use[87,88]. In contrast, plasma P-tau levels (measured by high sensitivity immunoassays) are increased by 3-7 times in cognitively impaired individuals with AD compared to cognitively unimpaired controls[84]. Measurement of plasma tau phosphorylated at various epitopes, including P-tau181, P-tau217 and P-tau231, has high accuracy for differentiating cognitive impairment due to AD from cognitive impairment caused by other conditions, with plasma p-tau217 consistently showing the highest diagnostic performance[89-95]. Further, plasma p-tau217 can be used to predict future development of AD dementia in nondemented symptomatic[96,97] and cognitively unimpaired individuals[98,99]. Several studies have also shown that plasma P-tau217 levels are highly concordant with amyloid PET positivity in both cognitively impaired individuals[91,100,101] and those who are cognitively unimpaired[91,102-104]. Using mass spectrometry to measure the p-tau217 to non-phosphorylated tau ratio (%p-tau217) can detect both amyloid PET and tau PET positivity with Areas Under the Receiver Operator Characteristics Curve of > 0.95. Further studies are needed to study how common medical co-morbidities, like kidney dysfunction or high body mass index affect plasma AD biomarker levels in different populations[105]. Current efforts are also underway to optimize plasma MTBR-tau243 as a fluid analog of tau PET[106].

While biofluid and PET measures of amyloid and tau can both be useful for diagnostic purposes, it is important to note that CSF and plasma measurements reflect the concentrations

of soluble forms of Aβ42 and P-tau, whereas PET radiotracers bind to aggregated protein inclusions. Several studies suggest that changes in CSF and plasma amyloid and P-tau may be detectable earlier than PET changes.[107,108] Although blood-based measures of amyloid, tau and neurodegeneration are promising, they are not yet approved by FDA for clinical use. For a comprehensive discussion on the current state of amyloid, P-tau and other blood-based biomarkers of neurodegeneration (e.g., neurofilament light-chain, glial fibrillary acidic protein, and others) see published Appropriate Use Recommendations[10].

7. Methods

7.1. Composition of expert workgroup

In June 2020, the AA and SNMMI convened a workgroup (hereinafter Workgroup) to update the AUC, with Avalere Health providing technical and editorial assistance. The Workgroup participated in teleconference meetings on a biweekly basis through August 2021. An additional one-time meeting was convened in August 2023 (see below).

In alignment with the Institute of Medicine's recommendations on group composition from its report *Clinical Practice Guidelines We Can Trust*, the AA and SNMMI established a multidisciplinary workgroup comprised of clinicians and other healthcare professionals with relevant expertise (list of members provided in Supplementary Appendix A)[109]. The 14 members included 4 neurologists (GDR, DK, OH, SS), 6 radiology/nuclear medicine physicians (JA, TB, KD, PHK, SM), 2 members double boarded in neurology and nuclear medicine (PH and KJ), 1 PET imaging methodologist (JCP), 1 neuro-ethicist (JHL), 1 pathology and laboratory medicine biomarker researcher (MEM). Twelve of the members were from the United States and two were from Europe (Spain and Sweden). Each member has published extensively on topics related to the key considerations around the use of amyloid and tau PET, such as dementia research, clinical practice and ethics, and biomarker test validation and clinical utilization.

7.2. Defining Scope and Key Research Questions

The process began with the Workgroup defining the scope and parameters of the AUC and developing key research questions to guide a systematic review of available evidence on amyloid and tau PET using the PICOTS approach (population, interventions, comparisons, outcomes, timing, and settings framework).[110] Supplementary Appendix B

The Workgroup then developed a list of 17 clinical scenarios that are encountered in clinical practice based on key patient groups in whom amyloid and/or tau PET may be considered as part of the diagnostic process. The Workgroup developed the clinical scenarios (Tables 2, 3 Section 8) through a confidential and formalized process adapted from the RAND and University of California, Los Angeles approach for AUC development.[111] The Workgroup began by reviewing the clinical scenarios in the 2013 amyloid PET AUC.[8] The Workgroup refined and updated the previous scenarios and added several new ones. This resulted in an updated set of scenarios applicable for the consideration of amyloid and tau PET presented in this document.

7.3. Systematic evidence review approach and findings

In a parallel effort, the Pacific Northwest Evidence-based Practice Center at Oregon Health & Science University (OHSU) conducted a systematic review of the literature. The primary purpose of the review was to summarize and assess the strength of evidence for the safety, diagnostic accuracy, and effect on patient outcomes of amyloid and tau PET, in cases posed in the key research questions listed in Supplementary Appendix C.

Searches for the review were conducted using OvidMEDLINE without revisions (December 2020) and supplemented with review of reference lists of relevant articles and systematic reviews. Database searches resulted in 3,238 potentially relevant articles. After dual review of abstracts and titles, 118 articles were selected for full-text dual review, and 18 studies (in 27 publications) were determined to meet inclusion criteria and were included in this review.

Two OHSU Evidence-based Practice Center staff reviewers independently assessed the quality of each study for inclusion. The strength of overall evidence was graded as high, moderate, low, or very low using the GRADE method (Grading of Recommendations, Assessment, Development, and Evaluations), based on the quality of evidence, consistency, directness, precision, and reporting bias. Specifically, we adapted criteria from the United States Preventive Services Task Force for randomized trials and cohort studies and from the Quality Assessment of Diagnostic Accuracy Studies[112] for studies of diagnostic accuracy (Appendix D). Discrepancies were resolved through a consensus process.

7.4. Rating of Clinical Scenarios

Using the evidence summary, their clinical experience and expertise, and their knowledge of research outside of the scope of the evidence review, the Workgroup employed a modified Delphi approach to reach consensus on ratings for each of the clinical scenarios. This approach consisted of an online survey and 2 rounds of virtual scoring. When rating each scenario, Workgroup members were asked to assess the benefits and risks to patients of using amyloid and tau PET imaging for the diagnosis of AD. In each scoring round, members were asked to assign to each clinical scenario a rating within ranges of appropriate, uncertain, or rarely appropriate for use of amyloid or tau imaging. A rating scale of 1 to 9 was used in each of the scoring rounds. The rating scale was defined as follows:

Score of 7 to 9, Appropriate:

9 = Highly confident that the scenario is appropriate
8 = Moderately confident that the scenario is appropriate
7 = Only somewhat confident that the scenario is appropriate

Score of 4 to 6, Uncertain:

6 = Uncertain, but possibility that the scenario is appropriate
5 = Uncertain, evidence is inconclusive or lacking
4 = Uncertain, but possibility that the scenario is rarely inappropriate

Score of 1 to 3, Rarely Appropriate:

3 = Only somewhat confident that the scenario is rarely appropriate
2 = Moderately confident that scenario is rarely appropriate
1 = Highly confident that the scenario is rarely appropriate

After each round of voting, resulting ratings given for each indication were tabulated and reported to the Workgroup. When an indication received all 14 Workgroup members' ratings in a single category of Appropriate, Uncertain, or Rarely Appropriate, that indication was considered to have reached consensus rating and was removed from the next round of voting. When voting for an indication resulted in all but one vote falling into the same category, that vote was considered an outlier and removed from the ratings.

The first round of voting was an anonymous online survey in which each member was asked to assign a single rating to each indication and enter a rationale for that rating. Workgroup members were then brought together for a series of 5 virtual meetings to complete the Delphi process. The virtual meetings began with a presentation of the first-round survey rating results and rationales. After extensive discussion, a second round of online voting was collected and tabulated. The results were reported to the Workgroup for further discussion. In this final round of deliberation, the Workgroup reached consensus on each indication, with all members rating the remaining indications as falling within the same category of Appropriate, Uncertain, or Rarely Appropriate.

7.5. Revisiting Clinical Scenarios involving AD therapeutics.

Significant advances in AD therapeutics occurred following the initial round of scenario scoring and prior to publication of these updated AUC. These include the publication of positive pivotal phase 3 clinical trials of the anti-amyloid monoclonal antibodies lecanemab[113] and donanemab[39], and traditional FDA approval of lecanemab in July 2023. Given the prominent role of amyloid PET (and to a lesser degree tau PET) in the clinical trials and future implementation of these therapies in clinical practice, the Workgroup reconvened in August 2023 to re-vote on Clinical Scenarios 14 and 15 which pertain to appropriateness of amyloid and tau PET to evaluate eligibility for, or monitoring response to, anti-amyloid therapeutics. Changes in scenario rankings between August 2021 and August 2023 are described in the text.

8. Appropriate Use Criteria for Amyloid and Tau PET Clinical Scenarios

8.1 Criteria for Clinical Scenarios

The following general principles served as the "litmus test" for appropriateness of amyloid or tau imaging across all clinical scenarios:

i) AD is considered as a likely etiology of cognitive impairment, but the etiology remains uncertain after a comprehensive evaluation by a dementia expert.
ii) Knowledge of the presence or absence of amyloid tau pathology is expected to help establish the etiology of impairment and alter management.

The Workgroup recommends that these principles be met in all patients referred for clinical amyloid/tau PET, across all clinical scenarios.

Anticipated impact on patient care

The guiding principle for clinicians considering amyloid and tau PET is that the results of these studies should have a direct impact on patient care by aiding diagnosis of the cause of cognitive decline and thus guide patient management. Establishing the cause of impairment can inform the care plan in a variety of ways, including:

1) Determining eligibility for drug treatment (e.g. approved and emerging molecular-specific therapies for AD, and approved AD symptomatic treatments that are not indicated in other disorders).
2) Counseling the patient and family regarding prognosis.
3) Reducing the need for alternative diagnostic tests for AD (e.g. CSF biomarkers) or initiating a work-up for non-AD conditions.
4) Helping inform decisions about patient safety (e.g., independent living, driving) and future planning (e.g. initiating or activating advance directives).

The Workgroup strongly emphasized the "value of knowing" in patients seeking care for cognitive changes[114,115], beyond concrete changes in patient management. Furthermore, amyloid and tau PET results can determine if a patient is eligible to participate in clinical research studies, including clinical trials.

In evaluating the utility of amyloid and tau PET, clinicians should consider patient-specific factors such as stage of impairment and age. Generally speaking, determining amyloid and tau status is more useful in early stages of impairment, and may be less impactful in patients already suffering from moderate-to-severe dementia. While tau PET positivity is more strongly linked to cognitive symptoms, the prevalence of amyloid PET positivity increases with age in cognitively unimpaired people, ranging in prevalence from ~10% at age 50 to ~45% at age 90[116,117]. In each age strata, the likelihood of amyloid PET positivity is 2-3 times higher in individuals who carry one or more copies of the apolipoprotein E ε4 risk allele (*APOE4*) than in *APOE4* non-carriers. Therefore, while a *negative* amyloid PET is always useful for ruling-out AD, the clinical relevance of a positive scan should take into account a patient's cognitive status, age, and the baseline prevalence of amyloid positivity in similarly aged, unimpaired individuals.

The decision to pursue amyloid or tau PET should result from shared decision-making between the ordering clinician, patient, and family, and should take into account the patient and family's desire to know amyloid/tau status in light of each possible test outcome (including positive, negative, or indeterminate results). While current data, obtained primarily in research settings, suggest that amyloid PET results can be disclosed safely and do not typically cause psychological harm, the individual mental health circumstances and support networks of the imaging candidate should be considered. Finally, as insurance coverage for amyloid and tau PET remains uncertain for many patients, the decision-making process should address the potential for co-payment and other out-of-pocket costs[118,119].

While the Workgroup sought to highlight the most common clinical scenarios under which amyloid and tau PET may be considered, a limited number of standardized scenarios can never capture the heterogeneity of patients in clinical practice, nor convey the complexity of clinical decision making for individual patients. Therefore, the criteria presented here should be considered as guidelines for clinicians, but not as a substitute for careful clinician judgment that considers the full clinical context for each patient presenting with cognitive complaints. In developing the scenarios, the Workgroup considered the degree to which PET results would inform patient diagnosis and care based on available literature most relevant to the scenario's clinical circumstance.

8.2 Clinical Scenarios and Appropriateness Ratings for Amyloid and Tau PET Imaging

The appropriateness scores (based on majority vote on the appropriateness scale at the conclusion of the Delphi process) for each clinical scenario are presented in Table 2. The

overall categorizations of each scenario as “appropriate,” “uncertain,” or “rarely appropriate” for each modality are presented in Table 3. *It is important to note that each of the ratings for the clinical scenarios presented below reflect the level of appropriate use of each modality by itself: amyloid imaging independent or in absence of tau imaging, and tau imaging independent or in absence of amyloid imaging.* The use of both modalities in combination is discussed later in the document (see Section 9). Additionally, while several studies have evaluated the clinical impact of amyloid PET, there is a paucity of data about clinical uses of tau PET, which to date has primarily been used in research studies. As a result, Workgroup recommendations regarding tau PET were often based on expert opinion and are not yet supported by empiric evidence. Therefore, the Workgroup generally had lower confidence in the appropriateness of tau PET in most scenarios.

Table 2: Clinical Scenarios and Appropriateness Ratings for Amyloid and Tau PET Imaging

Clinical Scenario	Rating	
	Amyloid PET	Tau PET
Clinical Scenario #1: Patients who are cognitively unimpaired who are not considered to be at increased risk for AD based on age, known APOE ε4 genotype, or multigenerational family history	**1**	**1**
Clinical Scenario # 2: Patients who are cognitively unimpaired but considered to be at increased risk for AD based on age, known APOE ε4 genotype, or multigenerational family history	**2**	**1**
Clinical Scenario # 3: Patients with subjective cognitive decline (cognitively unimpaired based on objective testing) who are <u>not</u> considered to be at increased risk for AD based on age, known APOE ε4 genotype, or multigenerational family history	**2**	**1**
Clinical Scenario # 4: Patients with subjective cognitive decline (cognitively unimpaired based on objective testing) who are considered to be at increased risk for AD based on age, known APOE ε4 genotype, or multigenerational family history	**6**	**2**
Clinical Scenario # 5: Patients presenting with mild cognitive impairment or dementia syndrome who are below 65 years and in whom AD pathology is suspected	**9**	**8**
Clinical Scenario # 6: Patients presenting with mild cognitive impairment or dementia syndrome which is often consistent with AD pathology (amnestic presentation) with onset at 65 years of age or older	**8**	**6**
Clinical Scenario # 7: Patients presenting with mild cognitive impairment or dementia syndrome that could be consistent with AD pathology but has atypical features (e.g., non-amnestic clinical presentation, rapid or slow progression, etiologically mixed presentation)	**8**	**7**
Clinical Scenario # 8: To determine disease severity or track disease progression in patients with an established biomarker-supported diagnosis of mild cognitive impairment or dementia due to AD pathology	**1**	**4**
Clinical Scenario # 9: Patients presenting with prodromal Lewy Body disease or dementia with Lewy Bodies.	**2**	**4**
Clinical Scenario # 10: Patients with MCI or dementia with recent CSF biomarker results that are conclusive (whether consistent or not consistent with underlying AD pathology)	**3**	**6**
Clinical Scenario # 11: Patients with MCI or dementia with equivocal or inconclusive results on recent CSF biomarkers	**8**	**6**
Clinical Scenario # 12: To inform the prognosis of patients presenting with mild cognitive impairment due to clinically suspected AD pathology	**8**	**7**

Clinical Scenario	Rating	
	Amyloid PET	Tau PET
Clinical Scenario # 13: To inform the prognosis of patients presenting with dementia due to clinically suspected AD pathology	**4**	**7**
Clinical Scenario # 14: To determine eligibility for treatment with an approved amyloid targeting therapy	**9***	**8***
Clinical Scenario # 15: To monitor response among patients that have received an approved amyloid targeting therapy	**8***	**5**
Clinical Scenario # 16: Non-medical usage (e.g., legal, insurance coverage, or employment screening)	**1**	**1**
Clinical Scenario # 17: In lieu of genotyping for suspected autosomal dominant mutation carriers	**1**	**1**

*Score of 1- 3 is Rarely Appropriate, Score of 4 - 6 is Uncertain, Score of 7- 9 is Appropriate

* - Scores reflect revoting in August 2023. See text for more details. Table 3.

Clinical Scenarios for Amyloid PET	Rating
Appropriate	
Clinical Scenario # 5: Patients presenting with mild cognitive impairment or dementia who are below 65 years and in whom AD pathology is suspected	9
Clinical Scenario # 6: Patients presenting with mild cognitive impairment or dementia syndrome which is often consistent with AD pathology (amnestic presentation) with onset at 65 years of age or older	8
Clinical Scenario # 7: Patients presenting with mild cognitive impairment or dementia syndrome that could be consistent with AD pathology but has atypical features (e.g., non-amnestic clinical presentation, rapid or slow progression, etiologically mixed presentation)	8
Clinical Scenario # 11: Patients with MCI or dementia with equivocal or inconclusive results on recent CSF biomarkers	8
Clinical Scenario # 12: To inform the prognosis of patients presenting with mild cognitive impairment due to clinically suspected AD pathology	8
Clinical Scenario # 14: To determine eligibility for treatment with an approved amyloid targeting therapy	9*
Clinical Scenario # 15: To monitor response among patients that have received an approved amyloid targeting therapy	8*
Uncertain	
Clinical Scenario # 4: Patients with subjective cognitive decline (cognitively unimpaired based on objective testing) who are considered to be at increased risk for AD based on age, known APOE ε4 genotype, or multigenerational family history	6
Clinical Scenario # 13: To inform the prognosis of patients presenting with dementia due to clinically suspected AD pathology	4
Rarely Appropriate	
Clinical Scenario #1: Patients who are cognitively unimpaired who are not considered to be at increased risk for AD based on age, known APOE ε4 genotype, or multigenerational family history	1
Clinical Scenario # 2: Patients who are cognitively unimpaired but considered to be at increased risk for AD based on age, known APOE ε4 genotype, or multigenerational family history	2
Clinical Scenario # 3: Patients with subjective cognitive decline (cognitively unimpaired based on objective testing) who are not considered to be at increased risk for AD based on age, known APOE ε4 genotype, or multigenerational family history	2
Clinical Scenario # 8: To determine disease severity or track disease progression in patients with an established biomarker-supported diagnosis of mild cognitive impairment or dementia due to AD pathology	1
Clinical Scenario # 9: Patients presenting with prodromal Lewy Body disease or dementia with Lewy Bodies.	2

Clinical Scenario # 10: Patients with MCI or dementia with recent CSF biomarker results that are conclusive (whether consistent or not consistent with underlying AD pathology)	3
Clinical Scenario # 16: Non-medical usage (e.g., legal, insurance coverage, or employment screening)	1
Clinical Scenario # 17: In lieu of genotyping for suspected autosomal dominant mutation carriers	1

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Clinical Scenarios for Tau PET	Rating
Appropriate	
Clinical Scenario # 5: Patients presenting with mild cognitive impairment or dementia who are below 65 years and in whom AD pathology is suspected	8
Clinical Scenario # 7: Patients presenting with mild cognitive impairment or dementia syndrome that could be consistent with AD pathology but has atypical features (e.g., non-amnestic clinical presentation, rapid or slow progression, etiologically mixed presentation)	7
Clinical Scenario # 12: To inform the prognosis of patients presenting with mild cognitive impairment due to clinically suspected AD pathology	7
Clinical Scenario # 13: To inform the prognosis of patients presenting with dementia due to clinically suspected AD pathology	7
Clinical Scenario # 14: To determine eligibility for treatment with an approved amyloid targeting therapy	8*
Uncertain	
Clinical Scenario # 6: Patients presenting with mild cognitive impairment or dementia syndrome which is often consistent with AD pathology (amnestic presentation) with onset at 65 years of age or older	6
Clinical Scenario # 8: To determine disease severity or track disease progression in patients with an established biomarker-supported diagnosis of mild cognitive impairment or dementia due to AD pathology	4
Clinical Scenario # 9: Patients presenting with prodromal Lewy Body disease or dementia with Lewy Bodies.	4
Clinical Scenario # 10: Patients with MCI or dementia with recent CSF biomarker results that are conclusive (whether consistent or not consistent with underlying AD pathology)	6
Clinical Scenario # 11: Patients with MCI or dementia with equivocal or inconclusive results on recent CSF biomarkers	6
Clinical Scenario # 15: To monitor response among patients that have received an approved amyloid targeting therapy	5
Rarely Appropriate	
Clinical Scenario #1: Patients who are cognitively unimpaired who are not considered to be at increased risk for AD based on age, known APOE ε4 genotype, or multigenerational family history	1
Clinical Scenario # 2: Patients who are cognitively unimpaired but considered to be at increased risk for AD based on age, known APOE ε4 genotype, or multigenerational family history	1
Clinical Scenario # 3: Patients with subjective cognitive decline (cognitively unimpaired based on objective testing) who are not considered to be at increased risk for AD based on age, known APOE ε4 genotype, or multigenerational family history	1
Clinical Scenario # 4: Patients with subjective cognitive decline (cognitively unimpaired based on objective testing) who are considered to be at increased risk for AD based on age, known APOE ε4 genotype, or multigenerational family history	2
Clinical Scenario # 16: Non-medical usage (e.g., legal, insurance coverage, or employment screening)	1
Clinical Scenario # 17: In lieu of genotyping for suspected autosomal dominant mutation carriers	1

755 *Score of 1- 3 is Rarely Appropriate, Score of 4 - 6 is Uncertain, Score of 7- 9 is Appropriate

756 * - Scores reflect revoting in August 2023. See text for more details.

8.3 Rationale for Clinical Scenario Appropriateness Ratings

Clinical Scenario 1

"Patients who are cognitively unimpaired who are not considered to be at increased risk for AD based on age, known APOE ε4 genotype, or multigenerational family history."

Consensus ratings

Amyloid = 1 (Highly confident that the clinical scenario is rarely appropriate)

Tau = 1 (Highly confident that the clinical scenario is rarely appropriate)

Amyloid

This scenario refers to cognitively unimpaired individuals (Section 3, Key Definitions) who are not at heightened risk of developing AD based on their age, *APOE* genotype or family history. As discussed above, a significant minority of such individuals will have positive amyloid PET scans. This "pre-clinical" stage of AD is an area of active investigation in both observational research and drug trials aimed at the prevention of future cognitive decline. Group-level analyses clearly indicate that amyloid PET-positive cognitively unimpaired individuals show accelerated cognitive decline compared to amyloid PET-negative cognitively unimpaired individuals, and are at heightened risk of developing MCI or dementia[120-122] (see Further Research Questions). However, at the individual patient level, there remains significant uncertainty about cognitive outcomes, and many amyloid-positive individuals do not develop clinically meaningful cognitive impairment even with relatively extended follow-up[123]. Currently, the uncertain clinical utility outweighs any benefits, although availability of proven preventive therapies would undoubtedly alter this judgment. Consequently, the Workgroup classified this indication as "Rarely Appropriate" (rating=1).

Tau

The vast majority of cognitively unimpaired individuals will show either completely negative tau PET or retention limited to the medial temporal lobe but sparing the neocortex; this is insufficient for a positive tau PET read based on the FDA-approved visual read criteria (Section 4, Figure 2)[124-127]. Tau PET uptake outside the medial temporal lobe is exceedingly rare in individuals who are amyloid PET negative. Emerging data suggest that individuals who are positive on both amyloid *and* tau PET are at higher risk of imminent cognitive decline compared to patients who are positive on just one of the two scans, or negative on both [81-83]. Up to 50% of amyloid-negative individuals show isolated tau PET uptake in the medial temporal lobe, and these individuals as a group show slower clinical decline compared to those with medial temporal tau *and* amyloid PET positivity[128]. Clearly, there is much yet to learn in terms of how best to apply tau PET along the continuum of cognitive functioning, alone and in tandem with amyloid imaging. Based on the paucity of data, especially regarding individual patient risk, the Workgroup classified tau PET as "Rarely Appropriate" in this scenario (rating=1).

Clinical Scenario 2

"Patients who are cognitively unimpaired but considered to be at increased risk for AD based on age, known APOE ε4 genotype, or multigenerational family history."

Consensus rating

Amyloid = 2 (Moderately confident that the clinical scenario is rarely appropriate)

Tau = 1 (Highly confident that the clinical scenario is rarely appropriate)

Amyloid

Amyloid positivity is associated with age, family history and APOE ε4 genotype[117,129]. Furthermore, age and *APOE4* genotype increase the risk of developing MCI or dementia in cognitively unimpaired individuals who are amyloid PET-positive[129-131]. These individuals may be more likely to seek memory specialist care to determine their risk of developing AD based on a family history or known genetic risk, as APOE testing is available through several straight-to-consumer genetic testing platforms. Current recommendations to ameliorate AD risk involve lifestyle factors that highlight the importance of physical, cognitive and social activity, diet, and adequate sleep, as well as optimizing treatment of vascular risk factors. These recommendations are universal regardless of an individual's risk of AD or amyloid status. As a result, the Workgroup concluded that amyloid PET would be "Rarely Appropriate" in this scenario, acknowledging that this is an evolving clinical decision point impacted by the need to know and by the possibility of future preventive pharmacologic interventions (rating=2).

Tau

As described above in scenario 1, currently available information about the utility of tau PET in this scenario is limited. The Workgroup concluded that tau PET is "Rarely Appropriate" in this scenario (rating=1).

Clinical Scenario 3

"Patients with subjective cognitive decline (cognitively unimpaired based on objective testing) who are not considered to be at elevated risk for AD based on age, known APOE ε4 genotype, or multigenerational family history."

Consensus ratings:

Amyloid = 2 (Moderately confident that scenario is rarely appropriate)
Tau = 1 (Highly confident that scenario is rarely appropriate)

Amyloid

Subjective Cognitive Decline (SCD) (Section 3, Key Definitions[132]) is very common. [133]In general, having SCD doubles the risk of developing mild cognitive impairment, [134,135]but the time lag from detection of SCD to MCI averaged 9.4 years (standard deviation 12.1 years) in one study. [136]In another cohort, incident MCI occurred in only 4/318 (1%) of SCD participants after 24 months[136]. Persons with SCD who seek evaluation in a memory clinic may be at higher risk of decline than individuals with SCD in the general population[137]. The clinically defined construct of SCD covers a surprisingly wide spectrum of phenomena that could be construed as representing a change from prior level of function. Some[134] but not all studies show that carriage of an APOE e4 allele increases risk of decline. Higher age, especially over age 80 years, is predictive of greater risk. On clinical grounds, the greater the consistency and breadth of cognitive complaints, the higher the likelihood of subsequent development of MCI. [135]Because of the long delay to and the highly variable likelihood of developing objective cognitive impairment, and the frequent presence of amyloid in an otherwise "normal" population, biomarker evidence of risk in SCD is necessarily of less certain prognostic value. Prognostic value of imaging biomarkers for AD in SCD is a complex function of length of the time horizon, age and the presence of comorbidities.

Compared to cognitively unimpaired persons, elevated amyloid is at least as common among persons >65 years old with SCD and may be slightly (but not dramatically) higher[138-141], is probably an interaction between the magnitude of SCD and amyloid burden[142,143], and elevated amyloid in this setting might predict more cognitive impairment[144]. The Workgroup members, in

noting that elevated amyloid conveyed little prognostic information and no actionable preventive interventions in persons with SCD who lacked an *APOE* e4 allele or multigenerational family history, felt that amyloid imaging was "Rarely Appropriate" (rating =2).

Tau

Because elevations in tau PET are so closely tied to the degree of cognitive impairment, the probability of meaningfully elevated tau PET (outside of the medial temporal lobe) is very low in persons with SCD[125] who by definition have normal objectively measured cognition. Therefore, tau PET was considered by the Workgroup to be "Rarely Appropriate" (rating = 1).

Clinical Scenario 4

"Patients with subjective cognitive decline (cognitively unimpaired based on objective testing) who are considered to be at increased risk for AD based on age, known APOE ε4 genotype, or multigenerational family history."

Consensus ratings:

Amyloid = 6 (Uncertain, but possibility that the scenario is appropriate)
Tau = 2 (Moderately confident that scenario is rarely appropriate)

Amyloid

As discussed in Scenario 3, persons with SCD who are older, carry the *APOE* ε 4 risk allele or have a multigenerational family history are at higher risk of developing MCI/dementia. In these individuals, SCD is more likely to represent the very earliest symptomatic stages of AD. Both positive and negative amyloid PET results may be informative to these individuals. Nevertheless, the degree of individual risk and the time-course for developing impairment are highly uncertain[83,120,130,137] ending clinical trial results in this population, preventive measures are limited to generally applicable lifestyle and health recommendations. Balancing these competing factors, the Workgroup was ultimately uncertain but endorsed the possibility that amyloid PET may be appropriate in this scenario (rating = 6).

Tau

Even in persons with risk factors such as older age, *APOE* e4 genotype or multigenerational family history, the probability of meaningfully elevated tau outside of the medial temporal lobe is very low in persons with SCD[139] who by definition have normal objectively-measured cognition. Therefore, tau PET was considered by the Workgroup to be "Rarely Appropriate" (rating = 2).

Clinical Scenario 5

"Patients presenting with mild cognitive impairment or dementia who are below 65 years and in whom AD pathology is suspected."

Consensus ratings:

Amyloid = 9 (Highly confident that the indication is appropriate)
Tau = 8 (Moderately confident that scenario is appropriate)

Amyloid

Young-onset dementia or MCI is defined as individuals who present with cognitive impairment before the age of 65.[145] A recent meta-analysis identified the prevalence of young-onset dementia in ages 30-64 to be 119.0 per 100,000 persons, with AD the leading cause, followed by frontotemporal dementia and vascular dementia.[146] Although the age cutoff of 65 is arbitrary, neuropathologic evidence suggests greater amyloid and tau burden in younger than older

individuals affected by AD.[147,148] As these working-aged individuals are in the prime of their life and are often supporting families, accurately diagnosing the cause of impairment is particularly important. The greater frequency of atypical (non-amnestic) clinical presentations in young-onset AD,[53] involving initial impairment in executive, language, visual, and (more rarely) behavior or motor function, often lead to delays in diagnosis or misdiagnosis that impacts treatment.[149,150] Given the lower frequency of co-existing pathologies in young-onset AD brains,[151] this population may be more likely to benefit from specific therapeutic agents targeting Amyloid and tau.

Amyloid PET is highly accurate in detecting AD neuropathology in patients with young-onset impairment. Rates of amyloid positivity are much lower in this age group in cognitively unimpaired people or patients with other neurodegenerative syndromes.[62,117,152] Conversely, in patients presenting clinically with an amnestic dementia, the prevalence of amyloid PET positivity *decreases* with increasing age due to a higher prevalence of non-AD neuropathologies that affect the medial temporal lobe (e.g., limbic-associated TDP-43 encephalopathy[LATE]).[117,153] Taken together, in the setting of a clinical syndrome suggestive of AD, amyloid PET positivity in young-onset dementia and MCI can be very helpful for ruling-in AD as the underlying neuropathology. Overall, the Workgroup concluded that amyloid PET is appropriate in this scenario (rating = 9).

Tau

Similarly, tau PET can be very helpful in detecting AD pathology in young-onset AD, with higher overall intensity and spatial spread of radiotracer retention compared to older patients at a similar disease stage.[154] Young-onset AD patients are more likely to be in advanced Braak stages of neurofibrillary pathology even at the MCI stage[154] increasing the likelihood of a positive tau PET scan.[36,155,156] Furthermore, variability in tau PET retention patterns closely mirror the variability seen in neurodegeneration patterns (via MRI or ^{18}F-FDG-PET) in young-onset AD.[152,157,158] Overall, based on current evidence the Workgroup concluded that tau PET is appropriate in this scenario (rating = 8).

Clinical Scenario 6

"Patients presenting with mild cognitive impairment or dementia syndrome which is often consistent with AD pathology (amnestic presentation) with onset at 65 years of age or older."

Consensus Ratings:

Amyloid = 8 (Moderately confident that scenario is appropriate)

Tau = 6 (Uncertain, but possibility that scenario is appropriate)

Amyloid

This scenario addresses cognitively impaired older adults who meet clinical criteria for MCI or a dementia syndrome that is amnestic in presentation and otherwise consistent with AD. In the original amyloid PET AUC, it was felt that amyloid PET would not add much value in individuals with dementia who have symptoms and an age-of-onset that is typical of AD[12]. However, subsequent reports from both observational studies and drug trials reported that 15% - 20% of individuals clinically diagnosed with late-onset probable AD dementia (including ~35% of APOE4-negative individuals) have negative amyloid PET[159,160]. Interestingly, the prevalence of amyloid PET positivity *decreases* with older age in patients with clinically typical amnestic dementia, likely reflecting an increasing prevalence of non-AD pathologies (e.g., vascular,

LATE) that can mimic AD clinically[117]. The rates of amyloid PET positivity in late-onset MCI range from 45%-70%[161], increasing with age and APOE ε4 genotype. Thus, there is almost always diagnostic uncertainty about the contribution of AD at the MCI stage. As discussed earlier, amyloid positivity is also common in cognitively unimpaired older adults and may be less specific among older patients in general. With advanced age comes an increasing likelihood that medical comorbidities and/or other co-existing pathologies (including overlapping neurodegenerative diseases) are contributing to the clinical presentation of cognitive impairment.[21] Nevertheless, a positive scan can, by virtue of satisfying the biomarker criteria required for a diagnosis of AD in persons with MCI or dementia, reduce the need for further diagnostic testing and heighten confidence in the management approach. In contrast, a negative scan can serve to rule out AD pathology as a cause of the observed impairment, triggering an alternative course for the diagnostic work-up and resulting management plan. In the Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) study, amyloid PET was positive in 55.3% of patients with MCI over age 65 and led to changes in patient management in 60.2% of MCI patients[159]. Based on these data, the Workgroup concluded that amyloid PET is appropriate in this scenario (rating = 8).

Tau

The Workgroup acknowledged the mounting data supporting the accuracy of tau PET for identifying pathological changes of AD and the high predictive value (i.e., correlation with a histopathologic reference standard) of such findings for patients presenting with dementia.[36,155] However, given the evidence that a positive ^{18}F-flortaucipir (FTP) tau PET (as rated by FDA-approved visual read criteria) reliably detects primarily advanced stages of tau pathology (Braak stages V-VI), a negative FTP tau PET visual read does not exclude the presence of clinically meaningful tau pathology (i.e., Braak stages III-IV), which represents the median tau pathology seen at autopsy in patients who died with MCI as well as in some patients who died with dementia[155]. Contrary to amyloid PET, the *positive predictive value* of FTP tau PET in patients with MCI or dementia is high, while the *negative predictive value* is uncertain, especially in older patients who may develop impairment at lower levels of tau pathology. The Workgroup also acknowledged the need for additional research on the utility of tau PET for clinical decision making in cognitively symptomatic patients at both the MCI and dementia stages of impairment. Ultimately, the Workgroup was uncertain but endorsed the possibility that FTP tau PET may be appropriate in this scenario (rating = 6).

Clinical Scenario 7

"Patients presenting with mild cognitive impairment or dementia syndrome that could be consistent with AD pathology but has atypical features (e.g., non-amnestic clinical presentation, rapid or slow progression, etiologically mixed presentation)."

Consensus ratings:

Amyloid = 8 (Moderately confident that scenario is appropriate)
Tau = 7 (Only somewhat confident that the scenario is appropriate)

Amyloid

Symptomatic cognitive impairment due to AD is clinically heterogenous. While memory loss is the most common presenting symptom, an estimated 20%-25% of patients present with non-amnestic syndromes, including primary changes in language,[162] visuospatial/visuoperceptual abilities,[163] executive functioning,[164] and (more rarely) changes in personality, behavior and motor functioning.[53,165,166] Autopsy studies suggest that AD is the most common underlying

neuropathology in patients presenting with the logopenic-variant of primary progressive aphasia (lvPPA)[167,168,] and posterior cortical atrophy (PCA) syndromes[50]. AD is also associated with a primary dysexecutive syndrome[164] and is the underlying neuropathology in ~25% of patients presenting with corticobasal syndrome (CBS)[169]. AD pathology is a relatively rare cause of the behavioral-variant of frontotemporal dementia[170,171] and nonfluent/agrammatic or semantic variants of PPA.[167,168] Furthermore, while AD is typically associated with a slow and insidious decline in cognition and function, some patients present with unusually rapid or slow progression.[54,172] Finally, mixed pathologies are increasingly common in older patients with MCI and dementia,[151,173] and these can manifest as clinically mixed presentations, with features of both AD and other dementia syndromes.

Patients presenting with atypical features often present a diagnostic challenge. Amyloid PET can be very helpful in excluding AD neuropathology in these patients[61,117,152]. A negative amyloid PET may increase clinical suspicion of a non-AD neurodegenerative process such as frontotemporal lobar degeneration (FTLD), particularly in patients presenting with focal, non-amnestic syndromes.[174] In patients with mild impairment and slow progression, negative amyloid PET raises the possibility of a potentially treatable, non-degenerative cause of impairment (e.g., primary medical, mood or sleep disorder).[161] Conversely, in patients with rapid progression, negative amyloid PET may suggest a non-AD neurodegenerative disease, prion disease, or autoimmune encephalopathy. A positive amyloid PET scan increases the likelihood that AD is the primary cause of impairment (particularly in lvPPA and PCA, in which the *a priori* likelihood of AD is high), or a contributing pathology in patients with etiologically mixed presentations. As always, the patient's age should be considered in interpreting the clinical meaningfulness of a positive amyloid PET result given the increasing prevalence of amyloid in cognitively unimpaired individuals with increasing age.[161] In the Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) study, amyloid PET was positive in 70.1% of patients with atypical dementia, and lead to changes in management in 63.5% of these patients[159]. Overall, the Workgroup concluded that amyloid PET was appropriate in this scenario (rating = 8).

Tau

As with amyloid PET, an "AD-like" tau PET binding pattern can help establish AD as a primary or contributing cause of impairment.[36,155,156] Furthermore, the spatial pattern of tau PET often matches brain regions that are clinically affected and show evidence of neurodegeneration on FDG-PET or MRI (e.g., greater involvement of occipital visual processing regions in PCA; greater left hemisphere involvement in lvPPA; greater binding in sensorimotor cortex in CBS due to AD),[175-178]increasing confidence that the underlying syndrome is due to AD. Additionally, high tau burden is associated with more rapid clinical progression, and low tau burden with slower progression.[171,179] Importantly, ^{18}F-FTP shows absent-to-low binding to tau aggregates in non-AD tauopathies (e.g., chronic traumatic encephalopathy or tau subtypes of FTLD),[180,181] and tau PET should not be used clinically to "rule-in" these conditions. Overall, the Workgroup concluded that tau PET was appropriate in this scenario (rating = 7).

Clinical Scenario 8

"To determine disease severity or track disease progression in patients with an established biomarker-supported diagnosis of mild cognitive impairment or dementia due to AD pathology."

Consensus ratings:

Amyloid = 1 (Highly confident that the clinical scenario is rarely appropriate)
Tau = 4 (Uncertain, but possibility that rarely appropriate)

Amyloid

This scenario relates to patients with an *existing* diagnosis of MCI or dementia due to AD pathology supported by biomarker evidence, e.g., a positive amyloid PET scan or CSF profile consistent with AD. Cross-sectional and longitudinal studies do not support the use of a subsequent amyloid PET to assess the degree of cognitive impairment or to monitor the rate of progression of the underlying AD pathological process. Both autopsy and PET studies have shown that Amyloid accumulation begins approximately two decades before onset of cognitive decline,[161] proceeds in a sigma-shaped fashion, is substantial at the MCI stage, and has typically approached a plateau at the stage of mild AD dementia.[130,182] There is little further accumulation as clinical manifestations progress, so serial scans are not helpful to monitor disease progression. Also, since there is little correlation between the level of brain amyloid and cognitive function in MCI or AD,[183] a repeat scan will not provide information on disease severity. Disease severity and progression in patients in this scenario should be tracked by clinical evaluation, including cognitive testing.

Because a subsequent amyloid scan provides no actionable information about disease severity or progression in patients with a biomarker-supported diagnosis of MCI or dementia due to AD pathology, the Workgroup concluded that amyloid PET is rarely appropriate in this clinical scenario (rating = 1).

Tau

In contrast to amyloid PET, autopsy and PET studies have shown that the level of cortical tau correlates with cognitive status and symptomatic disease stage[46,184] However, there are limited data on the clinical utility of serial tau scans. Therefore, the use of tau PET scans to track disease progression is uncertain. Currently, such a scan would not change patient management or add additional useful information beyond what is provided by serial clinical evaluations, e.g., with cognitive testing. It is possible that changes in tau PET could inform prognosis or treatment choices, but this remains to be demonstrated. The method of scan interpretation may play a role in considering the potential utility of serial tau scans. Both quantitative approaches and visual assessment of progression in the spatial pattern of tau could be useful. In addition, it should be noted that serial tau scans can have great value as a clinical research tool or in anti-AD drug development, as they can reflect disease progression or response to therapy. Overall, based on currently available data, the Workgroup was uncertain but endorsed the possibility that tau PET may be rarely appropriate in this scenario (rating = 4).

Clinical Scenario 9

"Patients presenting with prodromal Lewy Body disease or dementia with Lewy Bodies"

Consensus ratings:

Amyloid = 2 (Moderately confident that scenario is rarely appropriate)
Tau = 4 (Uncertain, but possibility that rarely appropriate)

Amyloid

Dementia with Lewy Bodies (DLB) is characterized by predominant deficits in executive and visuospatial functions, accompanied by additional core clinical features, including one or more spontaneous features of parkinsonism, fluctuating cognition, visual hallucinations, and rapid eye movement (REM) sleep behavior disorder.[185] Biomarkers contributing to the diagnosis are (1)

reduced binding of dopamine transporter radioligands in basal ganglia on single photon emission computed tomography (SPECT) or PET imaging; (2) low uptake of Iodine-131 meta-iodobenzylguanidine (^{123}I-MIBG) on myocardial scintigraphy; and (3) polysomnographic confirmation of REM sleep without atonia. Novel CSF seed amplification assays may provide direct evidence for aggregation of α-synuclein, the protein deposited in Lewy bodies and Lewy neurites[186]. The diagnosis of DLB is appropriate when dementia precedes or occurs concurrently with parkinsonism, whereas a diagnosis of Parkinson's disease with dementia (PDD) is more appropriate when dementia occurs in the setting of established Parkinson's disease (typically at least 1 year prior to dementia). Proposed criteria for prodromal MCI with LB (MCI-LB) include MCI (particularly involving executive or visuospatial domains with relative sparing of episodic memory) occurring in combination with core DLB clinical and biomarker features. Less well-characterized prodromal DLB presentations are delirium or marked fluctuations in consciousness, and late onset psychiatric presentations, including major depression or psychosis.[187] The defining neuropathology of DLB is widespread limbic and neocortical α-synuclein-containing Lewy bodies and Lewy neurites. Approximately 50% of patients with DLB are found to have core features of AD neuropathology, including diffuse and neuritic amyloid plaques and tau neurofibrillary tangles. Given the high prevalence of co-pathology, AD-specific biomarkers such as amyloid and tau PET are in general not useful in the diagnostic evaluation of DLB.

Amyloid PET is positive in over 50% of patients with DLB,[117] corresponding with the high prevalence of Amyloid plaques (diffuse more than neuritic plaques) at autopsy. Previous studies reported rates of 35%-40% amyloid PET positivity in patients with MCI-LB.[159,188] As in other disorders, amyloid positivity is more common with increased age and the presence of the APOE ε4 genotype. The pattern of amyloid tracer uptake is similar to AD, while binding intensity is on average intermediate between controls and dementia due to AD[189]. Overall, a positive amyloid PET does not help distinguish AD from DLB, although a negative scan can help exclude an AD diagnosis. Amyloid PET is more frequently positive in DLB than in PDD, and scan positivity is associated with lower cognitive performance and more rapid cognitive decline in PD, while results in DLB are mixed.[189] Amyloid PET results may not influence drug treatment, since acetylcholinesterase inhibitors are indicated in both DLB and AD, and anti-Amyloid antibody treatment would not be currently indicated in patients with clinical features of DLB. Overall, the Workgroup concluded that amyloid PET is rarely appropriate in the evaluation of suspected DLB in its fully established or prodromal stages (rating = 2).

Tau

Tau neurofibrillary tangle co-pathology is also often identified at autopsy in patients with PDD and DLB and contributes to cognitive impairment.[190,191] The tau PET signal in DLB is on average intermediate between AD dementia and controls, and higher than in PDD.[192-194]Tracer uptake is typically seen in temporoparietal and occipital cortex, with relative sparing of the medial temporal lobes. tau PET positivity is associated with amyloid PET positivity (although is also seen in some amyloid-negative patients) and correlates with lower cognitive performance.[195-198]A single small study of tau PET in prodromal DLB did not find elevated binding compared to controls.[199]Overall, tau PET is unlikely to differentiate between DLB, PDD and AD, though a positive scan increases the likelihood that AD pathology is contributing to cognitive impairment. As with amyloid PET, results of tau PET are unlikely to impact drug treatment. Overall, based on a relatively small number of available studies, the Workgroup was uncertain whether tau PET was appropriate in DLB, but felt it was possible that the indication was rarely appropriate (rating = 4).

Clinical Scenario 10

"Patients with MCI or dementia with recent CSF biomarker results that are conclusive (whether consistent or not consistent with underlying AD pathology)."

Consensus ratings:

Amyloid = 3 (Only somewhat confident that the scenario is rarely appropriate)
Tau = 6 (Uncertain, but possibility that the scenario is appropriate)

Amyloid

When determining abnormal levels of brain amyloid, the CSF Aβ42/Aβ40 and P-tau181/ Aβ42 ratios are highly congruent with the results obtained using amyloid PET imaging[200]. Consequently, there is generally no need to perform an amyloid PET scan in patients with clearly abnormal or normal CSF biomarker ratios. However, amyloid PET does offer additional information beyond CSF biomarker ratios. Whereas CSF assays measure concentrations of soluble Amyloid and P-tau monomers, amyloid PET characterizes the magnitude and spatial distribution of fibrillar Amyloid plaque deposition. CSF may also detect Amyloid-related changes prior to amyloid PET scan positivity. However, this additional information obtained from PET was felt to rarely lead to changes in diagnosis or management. Overall, the Workgroup concluded that amyloid PET in this scenario is rarely appropriate (rating = 3). While the group did not specifically discuss the utility of amyloid PET in patients with conclusive *plasma* AD biomarkers, similar principles would apply.

Tau

Few studies to date have evaluated the additional value of tau PET in patients with MCI and dementia with known CSF biomarker results. Even though CSF p-tau217 and p-tau181 concentrations correlate with the tau PET signal, the magnitude of correlation is modest; similar CSF concentrations can associate with highly variable degrees of tau PET uptake and spatial spread[80,81]. In cognitively impaired patients, tau PET is more strongly associated with cognitive function than CSF p-Tau concentration[75]. Accumulating evidence indicates that CSF levels of p-tau change earlier than the tau PET signal in preclinical AD[89,108], reaching a relative plateau during the symptomatic stage of the disease[201,202], while the tau PET signal continues to increase in patients with AD dementia[123,203]. Further, the fluid measures do not provide any regional information on tau pathology. Consequently, it is plausible that tau PET might add important information beyond CSF biomarkers, e.g., when it comes to defining AD subtypes[204] and prediction of subsequent cognitive decline[171], but additional studies are needed and the implications for patient care remain unclear. Overall, the Workgroup was uncertain but endorsed the possibility that tau PET may be appropriate in this scenario (rating = 6). While the group did not specifically discuss the utility of tau PET in patients with conclusive *plasma* AD biomarkers, similar principles would apply.

Clinical Scenario 11

"Patients with MCI or dementia with equivocal or inconclusive results on recent CSF biomarkers."

Consensus ratings:

Amyloid = 8 (Moderately confident that the scenario is appropriate)
Tau = 6 (Uncertain, but possibility that the scenario is appropriate)

Amyloid

Considering the bimodal distribution of the Aβ42/Aβ40 and P-tau/Aβ42 biomarker ratios, relatively few patients are close to the cut offs used to define abnormality[77,78]. However, in those patients with ratios very close to the established cut offs, an amyloid PET scan could be considered to determine the Aβ status more confidently. The two ratios mentioned above are more accurate than single CSF biomarkers for determining brain amyloid status. For example, increased CSF P-tau levels in patients with clearly normal CSF Aβ42/Aβ40 and P-tau/Aβ42 ratios do not normally warrant an amyloid PET scan. Overall, the Workgroup concluded that amyloid PET is appropriate in this scenario (rating = 8). While the Workgroup did not discuss the utility of amyloid PET in patients with equivocal or inconclusive *plasma* AD biomarkers, similar principles would apply.

Tau

In scenario 10 above, it was concluded that tau PET might have additional value independent of the outcome of already obtained CSF biomarker results. The Workgroup reached a similar conclusion for this scenario, expressing uncertainty but endorsing the possibility that tau PET may be appropriate in this scenario (rating = 6). While the Workgroup did not discuss the utility of tau PET in patients with equivocal or inconclusive *plasma* AD biomarkers, similar principles would apply.

Clinical Scenario 12

"To inform the prognosis of patients presenting with mild cognitive impairment due to clinically suspected AD pathology."

Consensus ratings:

Amyloid = 8 (Moderately confident that scenario is appropriate)
Tau = 7 (Only somewhat confident that the scenario is appropriate)

Amyloid

There is robust evidence of the prognostic value of amyloid PET for predicting future outcomes in patients with MCI whose clinical presentation is amnestic or otherwise consistent with AD. Although definitions of MCI subtypes are variable across studies, numerous reports have found that, allowing adequate follow-up duration, a majority of MCI patients with a positive amyloid PET scan will progress to AD dementia, while the risk of progression to AD dementia is significantly lower in those who are amyloid negative.[205-211]Overall, positive amyloid PET at baseline is associated with an average hazard ratio of ~3-4 (range: 2,1-11.4) for conversion to dementia in studies with 1-4.5 years of follow-up, after adjusting for confounding variables. The value of amyloid PET for informing prognosis in MCI is further supported by studies documenting the marked uncertainty and, in some cases, emotional turmoil that persons with MCI and their family care partners live with on a daily basis.[212] Learning whether or not AD pathology is present may lessen such uncertainty and enable clinicians and family care partners to guide patients with amyloid positivity to available resources for future planning. However, evidence is limited, and one study found that disclosure of amyloid PET results did not alter perceptions of ambiguity among patients and families impacted by MCI.[213] The Workgroup acknowledged that the "value of knowing" one's brain amyloid status in the context of MCI is a theoretical construct about which high level empirical evidence is lacking. Furthermore, individual rates of clinical progression in patients with amyloid-positive MCI are highly

variable[214], and the prognostic value of amyloid PET may be improved if combined with MRI or ^{18}F-FDG-PET as imaging markers of neurodegeneration.[61,189] While positive amyloid PET is useful in predicting *whether* individuals are likely to progress to dementia, it is not as useful at predicting *time to conversion*, and individuals with negative amyloid PET may still develop a non-AD dementia. Despite these caveats, the Workgroup concluded that amyloid PET is appropriate in this scenario (rating = 8).

Tau

Cohort studies have consistently found a positive tau PET scan to be associated with an increased likelihood of cognitive and functional decline in persons with MCI, suggesting the potential for such testing to inform prognosis in this clinical scenario. In a recent large, multi-site study, tau PET was a stronger predictor of longitudinal cognitive decline than amyloid PET or MRI cortical thickness in individuals with amyloid-positive MCI.[171] However, the use of tau PET in this scenario is currently being prospectively validated, and additional longitudinal studies are needed to further elucidate the prognostic value of tau PET in MCI. Overall, the Workgroup was somewhat confident that tau PET is appropriate in this scenario (rating = 7).

Clinical Scenario 13

"To inform the prognosis of patients presenting with dementia due to clinically suspected AD pathology."

Consensus ratings:

Amyloid = 4 (Uncertain, but possibility that the scenario is rarely appropriate)
Tau = 7 (Only somewhat confident that the scenario is appropriate)

Amyloid

The value of amyloid PET lies predominantly in confirming the presence of AD pathology as opposed to providing prognostic value. As a group, persons who meet clinical criteria for dementia due to AD and have a positive amyloid PET decline more rapidly than those who meet clinical criteria but have a negative amyloid PET.[165] This likely represents the fact that non-AD neuropathologies that mimic AD clinically (e.g., Limbic-predominant age-related TDP-43 encephalopathy [LATE]) are associated with less rapid decline. However, in amyloid-positive individuals with dementia, amyloid deposition has often plateaued and the burden or distribution of amyloid correlates poorly with baseline level of impairment or subsequent longitudinal decline.[215] Overall, the Workgroup was uncertain but endorsed the possibility that amyloid PET may rarely be appropriate in this scenario (rating = 4).

Tau

Neurofibrillary tangle burden associated with tau protein deposition correlates more closely with the severity of dementia than amyloid burden. In a recent large, multi-site study, tau PET correlated more strongly with longitudinal decline in the mini-mental state exam (MMSE) than amyloid PET (although less strongly than MRI cortical thickness) in individuals with amyloid-positive AD dementia.[171] Overall, acknowledging the limited available data, the Workgroup was somewhat confident that tau PET was appropriate in this scenario (rating = 7).

Clinical Scenario 14

"To determine eligibility for treatment with an approved amyloid targeting therapy."

Consensus ratings:

Amyloid = 9 (Highly confident that scenario is appropriate)

Tau = 8 (Moderately confident that scenario is appropriate)

Amyloid

Amyloid PET is often used to determine eligibility for enrollment in clinical trials testing anti-amyloid treatment for early AD[216-218], including the pivotal studies leading to FDA's accelerated approval of the anti-Amyloid monoclonal antibody aducanumab (EMERGE/ENGAGE trials) and full approval of the anti-Amyloid monoclonal antibody lecanemab (CLARITY-AD trial) for the treatment of MCI and mild dementia due to AD[219]. A third antibody, donanemab, recently reported positive phase 3 results (TRAILBLAZER-ALZ2 trial)[39]. In EMERGE, CLARITY-AD and TRAILBLAZER-ALZ2, treatment with an Amyloid-targeting monoclonal antibody was associated with slower cognitive and functional decline compared to placebo on primary and secondary clinical endpoints[220]. The FDA prescribing information for aducanumab and lecanemab require biomarker evidence of amyloid pathology (established via PET or CSF) prior to initiating therapy(lecanemab, aducanumab). Apart from its high diagnostic accuracy, amyloid PET exhibits some additional advantages over other amyloid biomarkers, such as low variability of the measure across centers and methods,[221] low individual variability in healthy subjects, and provision of information on extent and location of amyloid-pathology[48] which may be relevant for selecting candidates for amyloid-targeting therapies. Consequently, the Workgroup concluded that amyloid PET is appropriate in patients being evaluated for treatment with approved anti-Amyloid therapies (rating = 9). The final rating reflects an increase compared to the original rating in August 2021, which was still in the "Appropriate" range (*original* rating = 8).

Tau

The use of tau PET in anti-amyloid clinical trials is relatively limited to date. Elevated tau PET was required as an inclusion criterion in the TRAILBLAZER-ALZ2 trial of donanemab[39], while tau PET scans were acquired in a nonrandomized subset of participants in EMERGE/ENGAGE and CLARITY-AD.

The data available to date suggest that baseline tau PET may predict the magnitude of clinical benefit associated with amyloid removal by monoclonal antibodies. In TRAILBLAZER-ALZ2, clinical outcomes were evaluated separately in a baseline "low-medium" tau PET group and in the "combined population," the latter also including participants with baseline high tau PET. Overall, slowing of clinical decline was greater in the "low-medium" tau group than in the "whole population." A post-hoc analysis suggested limited clinical benefit compared to placebo in patients with "high" tau PET at baseline. An analysis of the tau PET sub-study from CLARITY-AD similarly showed that patients with the lowest baseline tau PET derived the greatest clinical benefit from treatment.[222] Collectively, the data suggest that amyloid removal may be most clinically beneficial in impaired individuals who are at earlier stages of tau spread as staged by PET. Based on these data, the Workgroup concluded that tau PET is appropriate in patients being evaluated for treatment with approved anti-Amyloid therapies (rating = 8). This final rating represents an increase from the initial rating in August 2021, which was in the "Uncertain" range (*original* rating = 5).

Clinical Scenario 15:

"To monitor response among patients that have received an approved amyloid targeting therapy."

Consensus ratings:

Amyloid = 8 (Moderately confident that scenario is appropriate)

Tau = 5 (Uncertain, evidence is inconclusive or lacking)

Amyloid

Serial amyloid PET scans can be used to measure amyloid plaque removal and thus confirm target engagement in clinical trials of amyloid lowering therapies targeting fibrillar forms of Amyloid[39,216,218,219,223-225]. Conversely, drugs that target soluble forms of Amyloid may show slowed accumulation (rather than reductions) of amyloid plaques[226]. The FDA determined that lowering of amyloid PET signal was a suitable surrogate biomarker "reasonably likely to predict a clinical benefit" as a basis for accelerated approval of aducanumab and lecanemab (prior to full approval of the latter based on demonstration of clinical efficacy in a phase 3 trial)[113,227]. Further work has suggested that, in the early symptomatic stage of AD, clinical response to amyloid-targeting monoclonal antibodies may be related to the magnitude of plaque reduction, the rapidity of plaque removal, or the ability to suppress amyloid levels below a threshold. All these outcomes are measured by amyloid PET changes in response to therapy[12,228-230].

While in EMERGE/ENGAGE and CLARITY-AD, active antibody treatment was maintained throughout the trials, in TRAILBLAZER-ALZ2 (and its phase 2 predecessor TRAILBLAZER-ALZ), the *duration* of antibody treatment was titrated to amyloid PET response, with patients switched from active treatment to placebo once their amyloid PET scans were in the negative range[39,218]. In both these phase 2 and 3 trials of donanemab, this approach to restricting treatment duration was sufficient to achieve a clinical benefit. Based on these emerging data, the Workgroup felt that measurement of amyloid reduction may be important in guiding management, and thus concluded that amyloid PET is appropriate for monitoring response in patients receiving approved amyloid targeting therapy (rating = 8). This represents an increase from the initial rating in August 2021, which was in the "Uncertain" range (*initial* rating = 6).

Tau

Consistently across trials, amyloid removal by amyloid-targeting monoclonal antibodies led to reductions in fluid (CSF and plasma) measure of phosphorylated tau. Data regarding the effects of amyloid removal on tau PET data are more limited and less consistent. In relatively small and nonrandomized subsets of patients enrolled in EMERGE/ENGAGE and CLARITY-AD, amyloid lowering treatment was associated with reductions or slowed progression of regional tau PET signal[113]. In the phase 2 TRAILBLAZER study, amyloid lowering slowed increases in regional (but not global cortical) tau PET, but these results were not replicated in the phase 3 TRAILBLAZER-ALZ2 trial.

Given that tau PET changes are thought to occur downstream of amyloid and have more established correlations with clinical outcomes, tau imaging has a great potential for gauging disease modification in patients treated with anti-amyloid therapies. However, based on very limited empiric evidence, the Workgroup was uncertain about the appropriateness of tau PET in this scenario (rating = 5). This rating reflects the initial rating in August 2021. Given limited additional data, the Workgroup elected *not* to vote again on this scenario in August 2023.

Clinical Scenario 16:

"Non-medical usage (e.g., legal, insurance coverage, or employment screening)."

Consensus ratings:

Amyloid = 1 (highly confident that the clinical scenario is rarely appropriate)
Tau = 1 (highly confident that the clinical scenario is rarely appropriate)

Amyloid and Tau

There is no evidence to suggest that amyloid or tau imaging is more informative than traditional neuropsychological or performance-based assessments to establish the presence, or evaluate the extent, of cognitive or functional impairment. Examples of non-medical usage include assessments of legal competency, employability, insurability and fitness to perform activities such as driving, piloting an aircraft, governing, or making financial decisions. The high prevalence of AD pathology in cognitively unimpaired older adults further underscores the inappropriateness of amyloid and tau PET for non-medical purposes. The committee therefore ranked both amyloid and tau PET as "rarely appropriate" in this scenario (rating = 1 for both).

Clinical Scenario 17:

"In lieu of genotyping for suspected autosomal dominant mutation carriers."

Consensus ratings:

Amyloid = 1 (highly confident that the clinical scenario is rarely appropriate)
Tau = 1 (highly confident that the clinical scenario is rarely appropriate)

Amyloid and Tau

Dominantly inherited AD (DIAD) is caused by autosomal dominant mutations in the amyloid precursor protein (*APP*), presenilin-1 (*PSEN1*) or presenilin-2 (*PSEN2*) genes. Pedigrees are typically characterized by early-onset of symptoms across multiple generations. The standard of care for evaluating potential mutation carriers includes a detailed clinical evaluation, including a family history, and referral to a genetic counselor for discussion of diagnostic or predictive genotyping. Amyloid PET in DIAD becomes positive approximately two decades prior to estimated year of symptom onset,[231-233] with cortical binding accompanied in some mutations by early and high binding in the striatum. Rarely, mutations lead to atypical conformations of amyloid (e.g., cotton wool plaques) that do not bind amyloid PET ligands. In contrast, tau PET in DIAD turns positive around the same time that cognitive changes are first detected.

In the future, amyloid and tau PET may be used to evaluate disease stage (i.e., onset and degree of amyloidosis and tau deposition) and potentially impact decisions about initiating specific therapies. Notably, amyloid targeting therapies have thus far not been shown to slow cognitive decline in DIAD[217]. Moreover, amyloid and tau PET should not be considered alternatives to genotyping, since absence of PET signal does not exclude a mutation, and conversely positive PET cannot confirm the presence of DIAD. The Workgroup therefore concluded that amyloid and tau PET are rarely appropriate in this scenario (rating=1 for both).

9. Value of Tau PET Imaging in Combination with Amyloid PET Imaging

The current AUC evaluated clinical scenarios for amyloid and tau PET separately for conceptual reasons, clarity, and because there was often insufficient evidence to evaluate the combined use of the two PET modalities. While this AUC will make no recommendations about the joint use of the two PET modalities, considerations of how the two complement each other will be

discussed here. We expect that future investigations will provide an empiric basis for optimizing their joint use.

The markedly different temporal and spatial profiles of amyloid and tau accumulation translates into different relationships between abnormal amyloid and tau PET images for the diagnosis of AD. The specific circumstances will determine which of the two PET tracers would be most helpful. Amyloid PET is a more sensitive biomarker for identifying persons who are early in the Alzheimer pathway. Amyloid PET has greater sensitivity in patients with MCI or earlier stages of impairment because tau PET abnormalities in CU, SCD or MCI persons are typically absent or very modest. In symptomatic persons, abnormal amyloid PET will not necessarily prove that AD is a relevant etiology if tau PET abnormalities are absent. As the topography of tau PET signal is closely correlated with spatial patterns of AD-related neurodegeneration and domain-specific cognitive performance, a topographically extensive tau PET pattern in a symptomatic person is highly likely to indicate that AD is a relevant etiology. If tau PET abnormalities were absent or spatially limited, the clinician could conclude that other etiologies are likely to be more relevant, even if elevated amyloid by PET was present.

There may be scenarios in which both tracers are required for decision-making. In a head-to-head study comparing the clinical utility of amyloid and tau PET, patients were randomized to receive amyloid or tau PET first (and the other modality second) as part of a diagnostic work-up[234]. Regardless of modality, the first PET scan led to a change in diagnosis in 28% of patients and the second scan changed diagnosis further in 18%-19%. The only modality-specific difference found was that a negative amyloid PET had a larger impact on diagnosis than a negative tau PET. In another recent study, the addition of tau PET led to a change in diagnosis in 7.5% of memory clinic patients with known amyloid status based on CSF[235]. In cognitively unimpaired individuals, the combination of positive amyloid and tau PET is associated with a greatly increased likelihood of conversion to MCI or dementia compared to individuals who are negative on both modalities, or positive just on one[99,126]. As discussed earlier, in the setting of therapeutic interventions targeted at reducing amyloid, it might be necessary to judge the burden of both amyloid and tau initially, and also to follow both for safety and efficacy reasons over the course of treatment.

10. Limitations of Evidence Review

The outside systematic review of the literature undertaken for this paper was presented more than 2 years prior to publication of these Appropriate Use Criteria. Since that time several additional papers evaluating the accuracy and clinical importance of amyloid and tau PET were published. The authors of these AUC have included these new papers in the bibliography when they were cited in the text; however, these papers were not subject to the same review process and grading as papers included in the initial systematic literature review.

As noted earlier, there are very limited data regarding the clinical utility of tau PET in comparison to amyloid PET, particularly pertaining to the impact of each modality on clinical decision making. This led to generally higher confidence in the utility of amyloid PET versus tau PET in most clinical scenarios.

Cognitive health disparities, defined here as preventable differences in the prevalence and risk of dementia due to AD and related disorders (AD/ADRD), are increasingly recognized to disproportionately negatively impact individuals from historically underrepresented racial and

ethnic groups. These groups have been markedly underrepresented in AD-related research, including in neuroimaging studies. Limited studies have generally found lower rates of amyloid PET positivity in African-Americans/Blacks, Hispanics/Latinx and Asian-American Pacific Islanders compared to non-Hispanic Whites, ranging from cognitively unimpaired research volunteers to patients with MCI and dementia[236-238], though the mechanisms that drive these observed differences are not well understood. Further studies of amyloid and tau PET in underrepresented populations are underway, as are efforts to enhance diversity across longitudinal AD/ADRD research cohorts[239].

Many of the studies comparing amyloid and tau PET to a neuropathological standard-of-truth were conducted in end-of-life patients. Studies validating PET-to-autopsy correlations in more clinically relevant memory clinic populations (i.e., the generally younger and less impaired individuals in which imaging would be considered) are needed. There is also increasing recognition that cognitive impairment in older individuals is very often related to multiple neuropathologies beyond Amyloid and tau (e.g., vascular contributions, Lewy bodies, LATE). More studies are needed to evaluate how copathologies impact the clinical interpretation of amyloid and tau PET results.

Finally, published evidence is often based on investigational studies conducted in research settings. When applying such research findings to general clinical patient populations, careful considerations need to be taken, given different pre-test probabilities of diseases in various clinical settings and possible inconsistencies in imaging quality, image interpretation accuracy, and other technical factors. It is important to reserve clinical judgments for individual patient considerations and specific clinical settings.

11. Further research questions

While much progress has been made in the clinical implementation of amyloid and tau PET, there are still many knowledge gaps that should serve as groundwork for future work. With the recent accelerated approval of Amyloid-targeting monoclonal antibodies, the field has entered a new era of molecular-specific therapies, and amyloid and tau PET are likely to play an increasingly important role in individuals being evaluated for these novel treatments. Beyond their diagnostic value, future work will undoubtedly focus on whether amyloid and tau PET can identify optimal responders to various treatments, and whether the duration of treatment can be calibrated based on longitudinal changes in PET. Especially in the context of longitudinal imaging, it will be important to determine whether quantitative approaches to image interpretation may enhance the current approach of visual reads. Some data do suggest a combination of visual and quantitative interpretation can improve the accuracy of reads, especially for less experienced nuclear medicine physicians and radiologists [32].PET quantification will likely be essential for gauging response to amyloid lowering therapies (and possibly in future tau lowering therapies[40,240]), in clinical practice, and for gauging disease progression.

To date, only one tau PET tracer (^{18}F-FTP) has been approved by the FDA for clinical use, based on a visual read method that highlights neocortical uptake and is insensitive to early-stage (but potentially clinically meaningful) tau pathology[36]. PET-to-autopsy studies are currently being conducted with additional tau PET tracers (e.g., ^{18}F-MK6240 and ^{18}F-PI2620), and employing alternative visual interpretation methods, including methods that identify binding that

is restricted to the medial temporal lobe[241-243]. These studies will determine whether alternative tau tracers or visual interpretation approaches are more sensitive to Braak Stages III/IV, which would impact future clinical recommendations. As noted earlier, augmenting visual reads with semi-quantification of PET signal in clinical practice could also broaden the utility of both amyloid and tau PET in guiding clinical care.

Few studies have evaluated the clinical impact of tau PET on patient diagnosis and management, as a single modality or in combination with amyloid PET[234,235]. Future clinical practice guidelines will determine the specific role of PET within the larger landscape of CSF and emerging plasma Amyloid and tau biomarkers. While much of the initial work on clinical utility has focused on diagnosis and patient management, data are beginning to emerge regarding the impact of amyloid PET on longer-term health outcomes, including inpatient and outpatient resource utilization, institutionalization and even mortality[244,245]. Finally, acknowledging the transformative impact of amyloid and tau PET on AD research and drug development, there remains a huge unmet need to develop molecular imaging markers for other protein aggregates, such as non-AD tauopathies, α-synuclein and TDP-43, to truly capture the complexity of brain pathologies that contribute to neurodegeneration and dementia.

Acknowledgements:

Contributors to acknowledge:

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Appendix A: Workgroup Acknowledgements of Conflict of Interest

The Alzheimer's Association, SNMMI, and Avalere rigorously attempted to avoid any actual, perceived, or potential conflicts of interest (COI) that might have arisen because of an outside relationship or personal interest of Workgroup members. Both organizations reviewed their own Industry Relationship Policies to ensure that the ensuing process adhered to both standards.

The Workgroup members were required to provide disclosure statements of all relationships that might be perceived as a real or potential COI. These statements were reviewed and discussed by the Workgroup co-chairs and updated and reviewed by an objective third party at the beginning of every Task Force meeting and/or teleconference. A table of disclosures for Task Force members and external peer reviewers can be found below, Table 4 and Table 6.

To adjudicate the conflicts of interest, the leadership from the Alzheimer's Association, SNMMI, and Avalere first determined the threshold for a real COI. Following consultation with various experts and review of other policies used, the team defined COIs as the following: An individual that had relationships with industry, including consulting, speaking, research, and other non-research activities, that exceed $5,000 in funding over the previous or upcoming twelve-month period.

The authors declare the following conflicts of interest:

Table 4: Workgroup Member Conflict of Interest

Workgroup Member	Affiliation	Conflicts of Interest
Javier Arbizu, MD, PhD	Professor and Chair, Department of Nuclear Medicine, University of Navarra Clinic	Clinical research for Araclon Biotech. Institution received research support from Life Molecular Imaging. Served as a consultant for Eli Lilly.
Tammie L. S. Benzinger, MD, PhD	Professor of Radiology and Neurological Surgery, Mallinckrodt Institute of Radiology	Consultant for Lilly, Biogen, Eisai, and J&J. Investigator initiated research funded by Siemens.
Kevin Donohoe, MD	Assistant Professor of Radiology, Beth Israel Deaconess Medical Center	The author declares that there is no conflict of interest
Oskar Hansson, MD, PhD	Professor of Neurology, Senior Consultant of Neurology, Lund University	OH has acquired research support (for the institution) from ADx, AVID Radiopharmaceuticals, Biogen, Eli Lilly, Eisai, Fujirebio, GE Healthcare, Pfizer, and Roche. In the past 2 years, he has received consultancy/speaker fees from AC Immune, Amylyx, Alzpath, BioArctic, Biogen, Bristol Meyer Squibb, Cerveau, Eisai, Eli Lilly, Fujirebio, Merck, Novartis, Novo Nordisk, Roche, Sanofi, and Siemens.

Peter Herscovitch, MD	Director, PET Department, NIH Clinical Center	Associate editor for Sage Publishing
Keith Johnson, MD	Director, Molecular Neuroimaging Massachusetts General Hospital, Professor of Neurology and Radiology, Harvard Medical School	Clinical trial for Cerveau Technologies and consultant for Novartis, Genentech, Jansson, Takeda, Merck, Prothena
David Knopman, MD	Professor of Neuroscience, Department of Neuroscience, Mayo Clinic	The author declares that there is no conflict of interest
Phillip H. Kuo MD, PhD	Professor, Medical Imaging, Medicine, and Biomedical Engineering, University of Arizona	Consultant and/or speaker for Blue Earth Diagnostics, Chimerix, Eli Lilly, Fusion Pharma, General Electric Healthcare, Invicro, Novartis, Radionetics, and Telix Pharmaceuticals. Recipient of research grants from Blue Earth Diagnostics and General Electric Healthcare.
Jennifer Hagerty Lingler, PhD	Professor, Vice Chair for Research Health & Community Systems, University of Pittsburgh	Consultant to Biogen and Genentech and has received research support from Avid Radiopharmaceuticals, a wholly owned subsidiary of Eli Lilly.
Satoshi Minoshima, MD, PhD	Professor and Chair, Department of Radiology and Imaging Sciences, University of Utah	Consultant and received educational donation from Hamamatsu Photonics, research grant from Hitachi, and education donation from Nihon Medi-Physics Co., Ltd
Melissa E. Murray, PhD	Professor of Neuroscience, Department of Neuroscience, Mayo Clinic	Consulted for AVID Radiopharmaceutical and receives research support from Eli Lilly
Julie C. Price, PhD	Professor of Radiology Massachusetts General Hospital	The author declares that there is no conflict of interest
Gil Rabinovici,	Professor, Departments of Neurology, Radiology & Biomedical Imaging University of California, San Francisco	Institution received research support from Avid Radiopharmaceuticals, GE Healthcare, Life Molecular Imaging and

MD		Genentech. Served as a consultant for Eli Lilly, Johnson & Johnson, Merck.
Stephen Salloway, MD, MS	Professor of Neurology and Psychiatry at the Warren Alpert School of Medicine at Brown University and Founding Director of the Butler Hospital Memory and Aging Program	Institution received research support for clinical trials from Biogen, Janssen, Eisai, Lilly, Genentech, and Roche. Served as a consultant for Merck, Novo Nordisk, and Acumen
Christopher J. Weber, PhD	Alzheimer's Association Director, Global Science Initiatives	Full-time employee of the Alzheimer's Association. No financial conflicts to disclose.
Maria C. Carrillo, PhD	Alzheimer's Association Chief Science Officer	Full-time employee of the Alzheimer's Association and has a daughter in the neuroscience program at USC. No financial conflicts to disclose.

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Appendix B: PICOTS Framework and Key Questions for Systematic Evidence Review

Population:

KQ 1**:** Persons who are cognitively unimpaired

KQ 2**:** Persons with subjective cognitive decline

KQ 3**:** Persons with mild cognitive impairment

KQ 4**:** Persons with atypical dementia presentation

KQ 5**:** Persons with AD dementia (mild, moderate, severe)

KQ 6**:** Persons with related dementia (i.e., caused by another neurodegenerative condition)

KQ 7**:** Persons with nondefinitive results on prior testing/imaging

KQ 8**:** Person with AD phenotype

Interventions:

All KQ**:** beta amyloid PET with florbetapir, florbetaben, flutemetamol

All KQ**:** tau PET with flortaucipir, soon-to-be approved agents (e.g., aducanumab)

Comparisons:

All KQ**:** Reference standard for Alzheimer's (e.g., pathological verification or clinical criteria)

All KQ: No amyloid PET

All KQ: No tau PET

Outcomes:

KQ 1,3**:** Diagnostic accuracy (sensitivity, specificity, and related measures); discrimination (AUROC)

KQ 2,4: Change in diagnosis, change in clinical management

KQ 5: Diagnostic accuracy, discrimination, risk estimates (e.g., odds ratio, relative risk, hazards ratio)

Study Considerations:

Excluded non-English studies

Excluded studies only published as abstracts

Table 5: Key Research Questions

Key Questions	Clinical Considerations and Sub-questions
[99]**Question 1:** 1. What is the accuracy of amyloid PET for detecting the presence of pathological changes that contribute to identifying persons with Alzheimer's disease?	a. What is the accuracy of amyloid PET in patients with Down syndrome or a relevant clinical syndrome (amnestic cognitive impairment, primary progressive aphasia, posterior cortical atrophy, dysexecutive cognitive impairment, or corticobasal syndrome)?
Question 2: What are the effects of amyloid PET versus no PET on clinical decision making?	
Question 3: What is the diagnostic accuracy* of tau PET for detecting the presence of pathological changes that contribute to identifying persons with Alzheimer's disease?	a. What is the accuracy of tau PET in patients with Down syndrome or a relevant clinical syndrome (amnestic cognitive impairment, primary progressive aphasia, posterior cortical atrophy, dysexecutive cognitive impairment, or corticobasal syndrome)?
Question 4: What are the effects of tau PET versus no PET on clinical decision making?	
Question 5: What is the prognostic value of amyloid/tau PET?	

Appendix C: Quality Rating Criteria Used for Systematic Review

Diagnostic Accuracy Studies Criteria

Patient selection: Was a consecutive or random sample of patients enrolled?

Index test(s): Were thresholds pre-specified?

Reference standard: Were the reference standard results interpreted without knowledge of the results of the index text?

Flow and timing

- Were all patients included in the analysis?
- Were any data discrepancies present?

Response options for all questions: Yes, no, unclear, or not applicable

Definitions of ratings based on above criteria:

1. High = Further research is very unlikely to change our confidence in the estimate of effect.
2. Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
3. Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
4. Very low = Any estimate of effect is very uncertain

Non-Diagnostic Accuracy Studies Criteria

Initial assembly of comparable groups

- Did the study attempt to enroll a random sample or consecutive patients meeting inclusion criteria (inception cohort)?
- Did the study use accurate methods for ascertaining exposures, potential confounders, and outcomes?

Maintenance of comparable groups

- Did the article report attrition?
- Is there important differential loss to follow-up or overall high loss to follow-up?

Measurements: equal, reliable, and valid

- Were outcomes pre-specified and defined, and ascertained using accurate methods?
- Were outcome assessors and/or data analysts blinded to treatment?

Definitions of ratings based on above criteria:

1. High = Further research is very unlikely to change our confidence in the estimate of effect.
2. Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
3. Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
4. Very low = Any estimate of effect is very uncertain

Appendix D: Additional Studies Reviewed

Author/Year	Study Design/N/ Country	Inclusion Criteria	Population	Clinical Outcomes	PET Technique/Notes
Altomare et al. 2021	RCT N=136 Switzerland	Cognitive complaints recruited consecutively and evaluated at the Geneva Memory Clinic; underwent diagnostic workup including clinical and neuropsychological assessments, MRI, and amyloid PET and tau PET within an ongoing prospective research study	Cognitive complaints recruited consecutively and evaluated at the Geneva Memory Clinic	Amyloid PET and tau PET, when presented as the first exam, resulted in a change of etiological diagnosis in 28%	Amyloid Tau PET
Amariglio et al. 2018	Prospective cohort N=279 US	Clinically normal	Mean age: 73.4 (6.1) Female sex: 59% MMSE: 29 (1.1)	Higher baseline SCC predicted more rapid cognitive decline on neuropsychological measures among those with elevated amyloid	11C PiB
Buckley et al./2016	Prospective cohort N=288 Australia	CN older adults who had undergone positron emission tomography (PET) Ab neuroimaging	CN Ab- Mean age: 69, female sex 54%; CN AB+ Mean age: 72,	In CN Amyloid+, subjects with high SMD did not exhibit significantly greater episodic memory decline than those with low SMD	n/a

			female sex 50%		
Buckley et al. 2019	Cross-cohort N=890 US	Clinically normal	Varies by Group	SCD increased odds of Amyloid+ by 1.58 relative to non-SCD	n/a
Burnham et al./2016	Longitudinal, N=573 Australia	Cognitively healthy	Mean age: 73.1 (6.2), Female:58%	50 (9%) healthy individuals were classified as A+N+, 87 (15%) as A+N−, 310 (54%) as A−N−, and 126 (22%) as SNAP. APOE ε4 was more frequent in participants in the A+N+ (27; 54%) and A+N− (42; 48%) groups than in the A−N− (66; 21%) and SNAP groups (23; 18%).	AD pathology was determined by measuring Amyloid deposition by PET, and neurodegeneration (N) was established by measuring hippocampal volume using MRI.
Soleimani-Meigooni et al. 2020	Prospective cohort N= 20 Unknown	N/A	Mean age: 61 Female sex: 8	PET-to-autopsy comparisons confirm that 18F-flortaucipir PET is a reliable biomarker of advanced Braak tau pathology in Alzheimer's disease	18F-flortaucipir
Donohue et al. 2017	Prospective cohort N=445 United States and Canada	Baseline Mini-Mental State Examination (MMSE) scores of 24 to 30 and Clinical Dementia Rating (CDR) Global and Memory Box scores of 0	Mean age: 74.0 (5.9) Female sex: 52%	Compared with the group with normal amyloid, those with elevated amyloid had worse mean scores at 4 years on the PACC (mean difference, 1.51 points, MMSE (mean difference, 0.56 points and CDR–Sum of Boxes (mean difference, 0.23 points	11C-PiB) and florbetapir
Dubois et al. 2018	Longitudinal observational N=318 France	Age 70-85 years with subjective memory complaints but unimpaired cognition and memory	Mean age: 76 (3.5) Mean MMSE: 28.67 (0.96)	88 (28%) of 318 participants showed amyloid β deposition and the remainder did not.	18F-florbetapir
Ebenau et al. 2020	Longitudinal N=693 Netherlands	Labeled as SCD	Mean age: 60 (9) Female sex: 41% MMSE: 28 (2)	Fifty-six participants had normal Alzheimer disease (AD) biomarkers (A–T–N–), 27% (n = 186) had non-AD pathologic change (A–T–N+, A–T+N–, A–T+N+), 18% (n	N/A

				= 122) fell within the Alzheimer continuum (A+T–N–, A+T–N+, A+T+N–, A+T+N+)	
Ghirelli et al. 2020	Longitudinal N=24 US	Participated in the Neurodegenerative Research Group, had 18F-flortaucipir and died with FTLD	N/A	Nine cases (37.5%) had Amyloid plaques	18F-flortaucipir Braak staging, Amyloid plaque, and neurofibrillary tangle counts, and semiquantitative tau lesion scores
Hanseeuw et al. 2019	Prospective cohort/Longitudinal N=1070 North America	N/A	Age range: 55-94	Amyloid predicted longitudinal changes in memory awareness, such that awareness decreased faster in participants with increased Amyloid burden.	Amyloid deposition was measured at baseline using [18F]florbetapir positron emission tomographic imaging
Jansen et al. 2015.	Meta-analysis 55 Studies N/A	Studies were included if they provided individual participant data for participants without dementia and used an a priori defined cutoff for amyloid positivity	N/A	The prevalence of amyloid pathology increased from age 50 to 90 years from 10% to 44% among participants with normal cognition; from 12% to 43% among SCI, and from 27% to 71% among MCI	N/A
Jack Jr. et al. 2019	Longitudinal cohort N=480 United States	Nondemented; had a clinical evaluation and amyloid positron emission tomography (PET) (A), tau PET (T), and magnetic resonance imaging (MRI) cortical thickness (N) measures between April 16, 2015, and November 1, 2017, and at least 1 clinical evaluation follow-up by November 12, 2018	Age range: 30 - 89	Among older persons without baseline dementia followed for a median of 4.8 years, a prediction model that included amyloid PET, tau PET, and MRI cortical thickness resulted in a small but statistically significant improvement in predicting memory decline over a model with more readily available clinical and genetic variables	Amyloid PET imaging was performed with Pittsburgh Compound B11 and tau PET with [18F]flortaucipir
Lesman-Segev et al. 2020	Observational N=101 United States	Enrolled in UCSF Memory and Aging Center or UCD	Mean age: 67.2 Female sex: 41	At autopsy, 32 patients showed primary AD, 56 showed non-AD neuropathology (primarily	Antemortem 11C-PiB and 18F- (FDG) PiB PET was rated as positive or negative for

		Alzheimer's Disease Center	MMSE: 21.9	frontotemporal lobar degeneration [FTLD]), and 13 showed mixed AD/FTLD pathology	cortical retention, whereas FDG scans were read as showing an Alzheimer disease (AD) or non-AD pattern
Leuzy et al. 2020	Diagnostic N=613 Sweden	Participated in the Swedish BioFINDER-2 study	N/A	RO948 F 18 outperformed magnetic resonance imaging and cerebrospinal fluid measures	RO948 F 18
Lopez et al. 2018	Longitudinal N=183 United States	Age 80 years and older, without dementia and participated in the Ginko biloba memory study from 2000 to 2008	N/A	Of the 183 participants, 30% were CN, 37% had MCI, and 33% were diagnosed with dementia at their last clinic visit.	11C PiB
Ossenkoppele et al. 2015	Meta-analysis N= N/A Location N/A	The MEDLINE and Web of Science databases were searched from January 2004 to April 2015 for amyloid PET studies	Data were provided for 1359 participants with clinically diagnosed AD and 538 participants with non–AD dementia. The reference groups were 1849 healthy control participants (with amyloid PET) and an independent sample of 1369 AD participants (with autopsy data).	The likelihood of amyloid positivity was associated with age and APOE ε4 status	N/A
Ossenkoppele et al. 2018	Cross-sectional N=719 South Korea, Sweden, and the United States	N/A	Mean age: 68.8 (9.2) Male Sex: 48.4%	The use of [18F]flortaucipir PET had an estimated sensitivity of 89.9% and specificity of 90.6% for	18F flortaucipir

				Alzheimer disease vs other neurodegenerative diseases	
Petersen et al. 2016	Longitudinal N=564 United States	Cognitively normal; invited to undergo imaging	N/A	At baseline, 179 (31.7%) individuals with elevated amyloid levels had poorer cognition in all domains measured, reduced hippocampal volume, and greater FDG-PET hypometabolism.	N/A
Petersen et al. 2019	Longitudinal N=763 United States	Enrolled in Mayo Clinic Study of Aging (MCSA), residents of Olmsted County MI, and participated in brain imaging	N/A	26% were A−N−, 15% were A+N−, 30% were A−N+, and 28% were A+N+	Pittsburgh Compound B
Roberts et al. 2018	Prospective cohort	Participants without dementia were randomly selected	Mean age: 71.3 (9.8) Male sex: 53.4% Prevalent MCI: 10.7%	Population-based prevalence of amyloid-positive status and progression rates of amyloid positivity provide valid information for designing AD prevention trials and assessing the public health outcomes of AD prevention and interventions	N/A
Villemagne et al. /2013	Prospective cohort N=200 Australia	Healthy controls, patients with mild cognitive impairment (MCI), and patients with AD	HC mean age: 73 (7.5); MCI mean age 73.4 (8.5); DAT mean age: 71.7(8.9)	At baseline, significantly higher Amyloid burdens were noted in patients with AD (2·27, SD 0·43) and those with MCI (1·94, 0·64) than in healthy controls (1·38, 0·39)	11C PiB
Villemagne et al. /2011	Longitudinal, N=206 Australia	Participated in the Melbourne Healthy Aging Study and the Austin Health Memory Disorders Clinic	n/a	At baseline, 97% of DAT, 69% of MCI, and 31% of HC subjects showed high PiB retention.	11C PiB
Rowe et al. 2014	Prospective cohort N= 183 healthy, 87 MCI Australia	Participated in the Australian Imaging, Biomarkers, and Lifestyle study	Healthy Mean age: 72 (7.26)	Thirteen percent of healthy persons progressed (15 to MCI, 8 to dementia), and 59% of the MCI cohort progressed to probable AD	11C PiB

			MCI Mean age: 73.7 (8.27) Healthy female sex: 51.9% MCI female sex: 49.4%		
Donohue et al. 2014	Observational N= N/A North America and Australia	Eligible participants will be 65 to 85 years of age at the time of screening, with a global Clinical Dementia Rating (CDR-G) score of 0, an MMSE score of 27 to 30, and a Delayed Recall score on the Logical Memory IIa subtest of 8 to 15 for participants with 13 or more years of education, or with an MMSE score of 25 to 30 and a Delayed Recall score on the Logical Memory IIa subtest of 6 to 13 for participants with 12 or less years of education	The participants analyzed had normal cognition and mean ages of 75.81, 71.37, and 79.42 years across the 3 studies	Analyses of at-risk cognitively normal populations suggest that we can reliably measure the first signs of cognitive decline with the ADCS-PACC	Varies
Knopman et al. 2012	Population-based N=296 United States	Participated in the Mayo Clinic Study of Aging diagnosed as cognitively normal who underwent brain MRI or [18F]fluorodeoxyglucose and Pittsburgh compound B PET, had global cognitive test scores, and were followed for at least 1 year	Mean age: 78 (75-82) Female sex: 130 (44%) MMSE: 28 (27-29)	Of the 296 initially normal subjects, 31 (10%) progressed to a diagnosis of mild cognitive impairment (MCI) or dementia (27 amnestic MCI, 2 non-amnestic MCI, and 2 non-AD dementias) within 1 year	[18F]fluorodeoxyglucose and Pittsburgh compound B PET
Jack Jr. et al. 2015	Cross-sectional observational N=1246 United States	Cognitively normal	N/A	Overall, memory worsened from age 30 years through the 90s	11C-PiB

Frings et al. 2018	Prospective cohort N=138 Location N/A	Patients referred for diagnostic imaging with [18F]FDG and [11C]PIB PET	N/A	[18F]FDG PET did not significantly predict conversion to AD	18F-FDG and 11C-PiB PET
Jansen et al. 2018	Cross-sectional N= Normal 2908; MCI 4133 Location Multiple	Participated in the multicenter Amyloid Biomarker Study	N/A	Among normal cognition, amyloid positively associated with low memory scores after age 70 but not associated with low MMSE. Among MCI, amyloid positively associated with low memory and low MMSE	N/A
Kemppainen et al. 2013	Prospective cohort N=24 Finland	Participated in earlier studies at Turku PET Centre	Six patients with AD (mean age 71.3), ten patients with amnestic MCI (mean age 70.4) and eight healthy control subjects (mean age 66.1)	The MCI group showed a significant increase in [11C]PIB uptake over time	11C-PiB
Lopez et al. 2014	Prospective cohort N=183 United States	Without dementia	Mean age: 85.2	The prevalence of b-amyloid deposition, neurodegeneration (i.e., hippocampal atrophy), and small vessel disease (WMLs) is high in CN older individuals and in MCI.	11C-PiB
Ma et al. 2014	Meta-analysis N= 352 (from 11 studies) Location N/A	Searches from MEDLINE (OvidSP), EMBASE (OvidSP), BIOSIS Previews (ISI Web of Knowledge), Science Citation Index (ISI Web of Knowledge), PsycINFO (Ovid SP), and LILACS (Bireme)	N/A	The included studies varied markedly in how the 11C-PIBPET scans were performed and interpreted	11C-PIB PET
Nordberg et al. 2012	Prospective cohort N=238	n/a	Control mean age: 67.4	[11C]PIB retention in the neocortical and subcortical	11C-PiB

	Europe		(6.3) MCI mean age: 67.5 (8.1) AD mean age: 69.2 (8.4)	brain regions was significantly higher in AD patients than in age-matched controls	
Ossenkoppele et al. 2014	Longitudinal N= AD 41, MCI 28, Control 19 Netherlands	Underwent 11C–PiB and 18F-FDG PET and MRI scans at baseline	Control mean age: 64 (9); MCI mean age 65 (9); AD dementia mean age 64 (6)	Baseline hypometabolism and atrophy were associated with poorer baseline performance on attention and executive functions	11C-PiB and 18F-FDG-PET and MRI
Trzepacz et al. 2014	Multivariate analysis N= ADNI 1 data United States	Varies	N/A	Of the 50 MCI subjects included in this study, 20 (40%) converted to Alzheimer's dementia within 2 years (converters) and 30 did not (nonconverters).	11C-PiB PET, MRI, and 18F-FDG-PET
Lowe 2020[44]	Prospective cohort N=26 United states	Cognitively impaired participants with abnormal amyloid based on amyloid PET, with anamnestic clinical presentation, participating in Mayo Clinical Study of Aging who passed away and underwent autopsy	Female sex: 38% Mean age: 79 (11.2) years Race: NR MMSE: 22 (7)	None (analysis limited to persons who died and under-went biopsy)	18F-flortaucipir Autopsy with IHC staining and BSS Braak tangle stage ≥4 and at least a moderate neuritic plaque score; or Braak tangle stage ≤3, at least a moderate neuritic plaque score, and no more than a moderate neuritic plaque score

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Appendix E: External Reviewers

The following individuals reviewed and provided feedback on this document prior to submission.

Table 6: External Reviewers

External Reviewer	Affiliation
Elizabeth C. Mormino, PhD	Wu Tsai Neurosciences Institute, Stanford University, Stanford, CA, USA; Department of Neurology and Neurological Sciences, Stanford University, Stanford, CA, USA.
Val Lowe, MD	Departments of Radiology, Mayo Clinic, Rochester, Minnesota, USA.
Philip Scheltens, MD, PhD	Alzheimer Center Amsterdam, Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc, Boelelaan 1118, 1081, HZ, Amsterdam, The Netherlands.
Chris Rowe, MD	Department of Molecular Imaging Research, Austin Health, Melbourne, Australia.
Henryk Barthel, MD, PhD	Department of Nuclear Medicine, University of Leipzig, Leipzig, Germany.
Susan Landau, MD	Helen Wills Neuroscience Institute, University of California, Berkeley, Berkeley, CA, USA.

Appendix F: Abbreviations

ADNC	Alzheimer's disease neuropathological changes
AA	Alzheimer's Association
AD	Alzheimer's Disease
APP	Amyloid precursor protein
Aβ	Amyloid-βeta
APOE4	Apolipoprotein ε4
AUC	Appropriate Use Criteria
CMS	Centers for Medicare and Medicaid Services
CL	Centiloids
CSF	Cerebrospinal fluid
CU	Cognitively unimpaired
COI	Conflicts of interest
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CBS	Corticobasal syndrome
DLB	Dementia with Lewy Bodies
DIAD	Dominantly inherited Alzheimer's Disease

FTP	Flortaucipir
FDG	Fluorodeoxyglucose
FDA	Food and Drug Administration
FTD	Frontotemporal dementia
FTLD	Frontotemporal lobar degeneration
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
IDEAS	Imaging Dementia—Evidence for Amyloid Scanning
I-131 MIBG	Iodine-131 meta-iodobenzylguanidine
DLB	Lewy bodies
LATE	Limbic-predominant age-related TDP-43 encephalopathy
lvPPA	Logopenic-variant of primary progressive aphasia
MRI	Magnetic resonance imaging
MCI	Mild cognitive impairment
MMSE	Mini-mental state exam
NFTs	Neurofibrillary tangles
NIA-AA	National Institute on Aging and Alzheimer's Association
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
OHSU	Oregon Health & Science University
PDD	Parkinson's disease with dementia
P-tau	Phosphorylated tau
PiB	Pittsburgh Compound-B
PICOTS	Population, Interventions, Comparisons, Outcomes, Timing, and Settings
PET	Positron Emission Tomography
PCA	Posterior cortical atrophy
PSEN1	Presenilin-1
PSEN2	Presenilin-2
REM	Rapid eye movement
SPECT	Single photon emission computed tomography
SNMMI	Society of Nuclear Medicine and Molecular Imaging
SUVR	Standardized uptake value ratio
SCD	Subjective cognitive decline
TDP-43	TAR DNA-binding protein 43
US	United States

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