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PET Imaging in Alzheimer Disease: Diagnostic and Prognostic Applications

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Abstract | Alzheimer Disease (AD) is a progressive neurodegenerative disorder characterized by amyloid-β deposition, tau pathology, synaptic dysfunction, neuronal injury and cerebral atrophy. Positron Emission Tomography (PET) has transformed AD evaluation by enabling in-vivo visualization of molecular and metabolic abnormalities. 18F-Fluorodeoxyglucose (FDG) PET evaluates cerebral glucose metabolism, amyloid PET identifies fibrillar amyloid-β and tau PET provides information about neurofibrillary pathology. This review examines diagnostic and prognostic applications of PET in AD, particularly in mild cognitive impairment, atypical dementia, differential diagnosis, disease staging, progression prediction and treatment selection. Evidence indicates that amyloid PET is highly useful for establishing amyloid pathology, whereas tau PET is more closely associated with disease stage and clinical severity. FDG PET remains valuable for identifying patterns of neurodegeneration and distinguishing AD from other dementias. With the emergence of disease-modifying anti-amyloid therapies, molecular confirmation has become increasingly relevant to treatment decisions. Important limitations include cost, availability, radiation exposure, tracer-specific limitations, mixed pathology and interpretation variability. Future integration of PET with MRI, blood biomarkers and artificial intelligence may improve individualized diagnosis, prognosis and therapeutic monitoring.

Key Words Alzheimer Disease, Positron Emission Tomography, Amyloid PET, Tau PET, FDG PET, Mild Cognitive Impairment, Dementia, Diagnosis, Prognosis

INTRODUCTION

Alzheimer Disease (AD) is the leading cause of dementia and is characterized by progressive cognitive and functional decline. Its biological processes begin years before overt dementia, creating an opportunity for biomarker-based diagnosis and early intervention. Traditional diagnosis relies on clinical assessment, cognitive testing, structural imaging and exclusion of alternative causes. PET has added a molecular dimension by allowing in-vivo visualization of amyloid, tau and cerebral metabolism. Contemporary guidance recognizes that these biomarkers can improve etiological confidence when the diagnosis remains uncertain [1]. FDG PET measures neuronal glucose metabolism, amyloid PET identifies fibrillar amyloid-β and tau PET visualizes aggregated tau pathology. The updated Alzheimer's Association/SNMMI appropriate-use criteria emphasize that PET should be ordered selectively when results are likely to influence diagnosis, prognosis, or management [2]. The emergence of anti-amyloid therapies has further increased the clinical importance of molecular confirmation because treatment decisions require evidence of amyloid pathology. Recent reviews describe PET as increasingly central to biologically based diagnosis, disease staging and therapeutic monitoring [3].

Biological Basis of PET Imaging

AD involves overlapping pathological processes including amyloid accumulation, abnormal tau, synaptic dysfunction, neuronal injury and atrophy. The AT (N)

framework conceptualizes Amyloid (A), Tau (T) and Neurodegeneration (N) as complementary biological domains. PET can contribute to all three: amyloid PET measures A, tau PET measures T and FDG PET provides a functional indicator of N. Amyloid PET emerged from early carbon-11 PiB studies and later fluorine-18 tracers expanded clinical availability. Tau PET subsequently provided a means of assessing the distribution of neurofibrillary pathology. Newer tracers aim to improve specificity and reduce off-target binding [4]. Because these modalities measure different biological processes, they should not be treated as interchangeable. Their greatest value is achieved when interpreted together with clinical findings, MRI, cognitive testing and fluid biomarkers.

FDG PET in Alzheimer Disease

18F-FDG PET measures cerebral glucose metabolism and provides an indirect marker of neuronal and synaptic dysfunction. AD commonly produces hypometabolism involving the posterior cingulate cortex, precuneus and lateral temporoparietal association cortices. The spatial pattern can help distinguish AD from other neurodegenerative disorders. The Alzheimer's Association specialty-care guideline recommends considering FDG PET when the etiological diagnosis remains equivocal after structural imaging, particularly in early MCI or atypical presentations [1]. The guideline reports sensitivity of approximately 80–99% and specificity of 63–98% for differentiating AD from frontotemporal lobar degeneration, while reported sensitivity and specificity for AD versus Lewy body disease are approximately 70–92% and 74–100%, respectively. FDG PET may also contribute to staging and prognosis because the magnitude and distribution of metabolic abnormalities correlate with neurodegenerative burden. However, interpretation becomes less useful in severe dementia, when diffuse hypometabolism can obscure disease-specific patterns [1].

Amyloid PET Imaging

Amyloid PET directly identifies fibrillar amyloid-β plaques. Available fluorine-18 tracers include florbetapir, florbetaben and flutemetamol. A positive scan indicates substantial amyloid pathology, whereas a negative scan substantially lowers the probability that significant amyloid pathology is responsible for a patient's cognitive syndrome. Amyloid PET is especially useful when clinical diagnosis is uncertain, including selected patients with MCI, atypical presentations, or early-onset cognitive impairment. However, amyloid positivity is not synonymous with dementia because amyloid pathology may occur in cognitively unimpaired older adults or alongside other diseases. Accordingly, PET findings must be interpreted within the clinical context [2]. The clinical relevance of amyloid PET has expanded with anti-amyloid therapies. Recent literature describes amyloid PET as increasingly important for confirming treatment eligibility and for quantifying biological treatment response using standardized approaches such as Centiloid scaling [3].

Tau PET Imaging

Tau PET provides a spatial representation of aggregated tau pathology and is particularly valuable because tau burden is more closely related to disease severity and cognition than amyloid burden alone. Tau pathology typically begins in medial temporal regions and spreads to association cortices as disease progresses. 18F-flortaucipir was the first FDA-approved tau PET tracer. Nevertheless, interpretation requires awareness of off-target binding and incomplete detection of all tau species. Next-generation tracers are being developed to improve specificity [4]. Current appropriate-use guidance recognizes selected applications of tau PET for disease staging, atypical presentations, prognosis and treatment-related decision-making [2]. Tau PET therefore has strong potential to move PET from binary diagnosis toward individualized biological staging.

PET and Prediction of Disease Progression

Prediction of progression from MCI to dementia is an important application of PET. Amyloid PET can identify individuals with underlying AD pathology, but amyloid positivity alone does not determine when dementia will occur. Prognosis is influenced by tau burden, cognitive impairment, neurodegeneration, age, vascular disease and other pathologies. FDG PET can provide prognostic information through the extent and distribution of hypometabolism, while tau PET may be particularly informative because tau accumulation more closely parallels clinical severity. Recent work also suggests that quantitative and multimodal approaches may improve prognostic accuracy compared with single biomarkers. Therefore, PET-based prognosis should be communicated probabilistically rather than as a precise individual prediction (Table 1).

Differential Diagnosis

PET can assist differentiation of AD from frontotemporal degeneration, dementia with Lewy bodies and other neurodegenerative disorders.

Table 1: Major PET Approaches in Alzheimer Disease

PET modality	Biological target	Main information	Primary application
18F-FDG PET	Cerebral glucose metabolism	Neuronal/synaptic dysfunction	Differential diagnosis and neurodegeneration
Amyloid PET	Fibrillar amyloid-β	Amyloid plaque burden	Biological confirmation of AD pathology
Tau PET	Aggregated tau	Neurofibrillary pathology and distribution	Staging and prognosis
Quantitative PET	Tracer uptake metrics	Objective longitudinal measures	Research and treatment monitoring

Table 2: Diagnostic and Prognostic Roles of PET

Clinical question	FDG PET	Amyloid PET	Tau PET
Confirm AD pathology	Indirect	Strong	Strong but stage-dependent
Differential diagnosis	Strong	Moderate–strong	Emerging
MCI risk assessment	Moderate	Useful	Potentially strong
Disease staging	Moderate	Limited	Strong potential
Treatment selection	Indirect	Important	Increasing role
Treatment monitoring	Research	Useful in selected settings	Emerging

Table 3: Typical PET Patterns in Major Neurodegenerative Disorders

Disorder	FDG PET	Amyloid PET	Tau PET
Alzheimer disease	Posterior temporoparietal/posterior cingulate hypometabolism	Usually, positive	AD-pattern distribution
Frontotemporal degeneration	Frontal/anterior temporal hypometabolism	Usually, negative	Usually negative for AD-pattern tau
Dementia with Lewy bodies	Often occipital hypometabolism	Variable	Usually lacks typical AD pattern
Vascular cognitive impairment	Patchy/variable abnormalities	Variable	Usually negative for typical AD tau
Mixed pathology	Variable	May be positive	May show AD-pattern tau

FDG PET is particularly useful because diseases demonstrate different metabolic patterns. AD typically produces posterior temporoparietal and posterior cingulate hypometabolism, whereas frontotemporal disorders more often show frontal and anterior temporal abnormalities. Lewy body disease may show occipital hypometabolism. Amyloid PET can help determine whether AD amyloid pathology is present, while tau PET can demonstrate whether tau distribution is consistent with AD. Nevertheless, mixed pathology is common in older patients and PET findings should be integrated with clinical history, examination, MRI and other biomarkers [1] (Table 2).

PET and Treatment Decisions

The emergence of disease-modifying anti-amyloid therapies has changed the clinical role of PET. Updated appropriate-use criteria emphasize that amyloid and tau PET should be performed when results are expected to influence care, including clarification of diagnosis and assessment of eligibility for disease-modifying treatment [2]. Amyloid PET is particularly relevant because anti-amyloid therapy targets Aβ pathology. Tau PET may provide complementary information about disease stage and expected clinical benefit. Recent reviews emphasize that PET is shifting from a confirmatory research biomarker toward an active component of therapeutic decision-making and treatment monitoring [3] (Table 3).

Quantitative PET and Artificial Intelligence

Visual PET interpretation remains important, but quantitative methods can improve reproducibility and detect subtle abnormalities. Common approaches include standardized uptake value ratios, cortical composite measures, voxel-based analysis and Centiloid scaling. Quantification is increasingly relevant for longitudinal treatment monitoring. Artificial intelligence and machine learning may further enhance PET by integrating imaging with MRI, cognitive testing, APOE status and blood biomarkers. However, models require large and diverse datasets and external validation before widespread clinical adoption. The emerging multimodal approach is likely to combine molecular imaging with accessible blood biomarkers rather than rely on any single test.

Limitations

PET has several limitations. First, amyloid positivity is not equivalent to clinical AD dementia. Second, tau tracers differ in their binding properties and may demonstrate off-target signal. Third, PET is expensive and not universally available. Fourth, radiation exposure limits unnecessary repeated imaging. Fifth, interpretation varies with tracer, scanner, acquisition protocol, reference region and quantitative threshold. Mixed pathology is another major challenge. A patient may have AD pathology together with vascular disease, Lewy body pathology, TDP-43 proteinopathy, or other conditions. PET should therefore be interpreted as one component of a multimodal diagnostic process. The appropriate-use criteria explicitly emphasize clinical correlation, technical quality and patient-centered decision-making [2].

Future Directions

Future PET research is likely to focus on next-generation tau tracers, improved imaging quantification, multimodal artificial intelligence and integration with blood biomarkers. The development of blood-based biomarkers may allow PET to be reserved for cases in which molecular localization or therapeutic decision-making requires additional certainty. Recent reviews emphasize that tau PET retains a unique advantage because it provides topographic information that fluid biomarkers cannot provide [5]. Quantitative amyloid and tau PET may also become increasingly relevant for monitoring biological response to therapy. These developments could establish a more personalized imaging framework in which the choice of tracer is determined by the clinical question rather than by a one-size-fits-all diagnostic pathway.

DISCUSSION

PET has transformed AD from a condition diagnosed largely through clinical phenotype into a disease increasingly characterized through biological biomarkers. Amyloid PET provides strong evidence of fibrillar amyloid

pathology, tau PET provides information about neurofibrillary disease distribution and stage and FDG PET provides a functional map of neurodegeneration. Their roles are complementary rather than interchangeable. The strongest current clinical rationale for PET is in patients with objectively established cognitive impairment in whom diagnostic uncertainty persists and the result is expected to change management. This principle is central to the updated 2025 appropriate-use criteria [2]. The expanding use of disease-modifying therapies further strengthens the value of biological confirmation. However, cost, access, radiation, tracer limitations and mixed pathology mean that PET should not be used indiscriminately. The future is likely to involve a tiered pathway in which clinical assessment and blood biomarkers identify patients who may benefit from confirmatory PET, followed by multimodal interpretation for diagnosis, prognosis and treatment planning.

CONCLUSIONS

PET imaging is an important component of modern Alzheimer disease diagnosis and prognosis. FDG PET contributes particularly to differential diagnosis and characterization of neurodegeneration. Amyloid PET provides direct evidence of fibrillar amyloid pathology and is increasingly important for treatment-related decisions. Tau PET provides complementary information about disease distribution, stage and prognosis. PET is most valuable when interpreted within a comprehensive clinical and biomarker framework. Continued improvements in tracer specificity, quantitative analysis, artificial intelligence and integration with blood biomarkers are likely to increase the precision and clinical utility of PET. Overall, molecular PET imaging is helping move AD care toward earlier, biologically informed and increasingly personalized diagnosis and treatment.

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