Review

Dedicated Brain PET in the Emerging Care Pathways of Alzheimer's Disease

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Dedicated Brain PET in the Emerging Care Pathways of Alzheimer's Disease

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Abstract

In the era of emerging blood-based biomarkers and continuously evolving diagnostic frameworks for Alzheimer's disease (AD), dedicated brain positron emission tomography (PET) has re-emerged as a significant advancement in molecular neuroimaging and clinical practice. Compact, standalone brain PET systems are designed to overcome the economic and infrastructural limitations of conventional whole-body PET/CT scanners, offering reduced cost, smaller footprint, and increased accessibility without compromising diagnostic image quality. Leveraging advances in detector technology, silicon photomultipliers, and optimized correction and reconstruction algorithms, these systems achieve image performance that is clinically non-inferior for neurological applications. With the advent of disease modifying anti-amyloid therapies and the growing demand for biomarker-based early and differential diagnosis of AD, integration of dedicated brain PET into the new care pathways for diagnosis and disease management seems increasingly relevant. This review critically evaluates the clinical opportunities and challenges associated with the implementation of recently commercialized compact brain PET devices in the clinical practice, in alignment with current guideline-based biomarker strategies in early diagnosis and management of AD. Despite advantages such as smaller footprint, simplified operation, and cost-effectiveness, widespread adoption will require overcoming barriers including reimbursement models, clinical education, and harmonization of acquisition and quantification standards. Looking ahead, artificial intelligence holds promise to further streamline scanner operation, enable automated corrections, support dose optimization, and ensue standardized image interpretation across decentralized care settings.

Keywords: positron emission tomography (PET); dedicated brain PET; alzheimer's disease; molecular neuroimaging; biomarker-based diagnosis; diagnostic pathways

1. Introduction

Over the past several decades, positron emission tomography (PET) has become an indispensable imaging tool in clinical neurology [1] and in advancing the understanding of neurodegenerative diseases [2]. Brain PET images provide information on cerebral perfusion, metabolism, and receptor activity—parameters that are often affected earlier in neurodegenerative disease progression than structural brain changes [2]. Conventional PET scanners, originally designed for whole-body imaging with a large bore size and field of view (FOV), are not optimized for the requirements of imaging the human brain, which limits their performance when focused on the relatively small, complex anatomy of the human brain, as well as their accessibility, as only large facilities with specialized imaging centers can afford the cost and space to install and offer this modality [3].

Dedicated standalone brain PET systems have emerged over the last decades as a transformative solution to address these challenges and to meet the urgent need for earlier diagnosis and management of neurodegenerative diseases amid their growing global burden [3,4]. These systems are optimized specifically for neuroimaging featuring smaller detector geometries, smaller bore size and FOV, tailored reconstruction algorithms for cerebral applications, and some with compact

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portable designs that lower purchase and operational costs, thereby expanding accessibility to smaller clinical settings [4].

Alzheimer's disease (AD) is the leading cause of dementia worldwide [5] and within the European Union (EU) [6]. Its prevalence continues to rise with increasing life expectancy, yet AD remains underdiagnosed due to challenges in establishing accurate and early diagnosis [5.6]. Pathologically, AD is characterized by features such as the accumulation of amyloid-beta (Aβ) plaques, tau neurofibrillary tangles, and progressive neuronal loss and synaptic dysfunction [7]. These changes begin years—if not decades—before cognitive symptoms appear, establishing AD as a continuum of pathologies, ranging from mild cognitive impairment (MCI) to full-onset dementia [8]. The dissociation between pathology and clinical presentation has fueled recent interest in biomarker-based diagnosis. One widely adopted framework is the A/T/N classification, categorizing AD biomarkers into three groups: "A" referring to the value of Aβ-amyloid biomarker (amyloid PET or Cerebrospinal fluid (CSF) Aβ42); "T," the value of a tau biomarker (CSF p-tau, or tau PET); and "N," biomarkers of neurodegeneration or neuronal injury ([^{18}F]-fluorodeoxyglucose (FDG)–PET, structural Magnetic Resonance Imaging (MRI), or CSF total tau) [9] . Reflecting these advances, the National Institute on Aging (NIA) and the Alzheimer's Association (AA) published revised diagnosis and staging criteria of AD [10]. These updates were driven by: 1) regulatory approval of disease-modifying therapies (DMTs) targeting core AD pathology, necessitating precise assessment of biomarkers indicating the presence of AD pathology [11]; 2) the development of blood-based markers (BBM) with some (not all) assays exhibiting accurate diagnostic performance; 3) the recognition that imaging, CSF, and BBM within the AT(N) framework may be interchangeable for certain but not all intended uses [10].

Brain PET imaging has played a pivotal role in AD research and clinical practice [12]. [^{18}F]- FDG PET, as a well-established imaging biomarker, measures regional glucose metabolism and is particularly valuable for differentiating dementia subtypes [13]. In parallel, amyloid and tau PET imaging have transformed our understanding of AD progression and staging, with direct implications for clinical management [14]. Amyloid PET enables in vivo visualization of amyloid deposition and is valuable in distinguishing between etiologically distinct forms of neurodegeneration, particularly in cases of mixed pathologies, making them an important diagnostic tool in the diagnostic workflow [15].

With the growing focus on cost-effective early diagnosis of AD, the emergence of BBM, and a shift toward earlier identification of individuals at risk of AD [16], the relevance of cost-effective brain-optimized PET systems is amplified, as it has also already been discussed that PET imaging and fluid biomarkers provide complementary and non-redundant value in AD diagnostic [17]. Future AD diagnostic pathways may combine plasma-based screening with imaging-based confirmation, balancing accessibility with robust diagnostic validation [17].

This review aims to synthesize the integration of current commercially available dedicated brain PET imaging systems into clinical practice. We evaluate their potential role alongside novel biomarkers and disease-modifying therapies, and consider how technological innovation may enable the transition of PET from a specialized imaging modality to a routine pillar of neuroimaging practice—where multi-biomarker strategies are required for early diagnosis, patient stratification, and therapeutic monitoring in AD.

2. Clinically Available Compact Standalone Brain PET Systems

The design of dedicated brain PET scanners over the past decades has revolved around three primary goals: increasing performance within the cranial volume, particularly spatial resolution or sensitivity [18,19]; developing compact and portable designs that minimise space requirements, such as devices with upright seated patient positioning; and reducing the costs of the scanner compared with the conventional whole-body systems [20].

Among standalone brain PET systems, some high-performance platforms such as NeuroEXPLORER or Ultra-High Resolution (UHR) scanners have remained investigational research

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devices [18,19], whereas some designed specifically for clinical usability have received the U.S. Food and Drug Administration (FDA) clearance or the European CE ("Conformité Européenne") mark and are commercially available [20,21]. This remains a rapidly evolving field, with additional innovative technologies expected to reach the market. The aim of this review is therefore not to provide an exhaustive catalogue of existing brain PET systems or a detailed comparison of technical specifications- topics already reported elsewhere [20], but to emphasis the clinical opportunities these systems represent, particularly in reshaping the diagnosis workflow of early AD.

2.1. NeuroLF®

Among commercially available systems, NeuroLF® (Positrigo AG, Switzerland) [20,22] is notable as one of the first dedicated brain PET scanners to obtain both FDA 510(k) clearance (July 2024) and CE marking (October 2024) [AuntMinnie.com Clinical News (2024)] for routine clinical use in disorders such as AD, epilepsy, brain tumors, and Parkinson's disease. NeuroLF is actively marketed in both Europe and the United States and is specifically designed for ultra-compact, upright seated patient positioning with head-only imaging, while offering lower purchase and operational costs compared with whole-body PET/CT.

Preliminary published data [20,22,23], describe NeuroLF dimensions of 170 × 210 × 80 cm^3 (H × L × W) with recommended installation room size of: 2.7 × 4 m^2. The scanner has a bore diameter of 260 mm; and detector ring diameter of 271 mm with an axial FOV of approximately 163 mm. Detectors are composed of LYSO crystals (3.19 × 3.19 × 10 mm^3) arranged in blocks of 6 × 6 arrays and coupled to 3 × 3 arrays of silicon photomultipliers (SiPMs) [20,23]. The reported spatial resolution full width at half maximum (FWHM) measured with National Electrical Manufacturers Association (NEMA) NU-2 2018 was 2.7 mm and 3.5 mm at 1cm and 10 cm respectively [23] Attenuation correction is performed using template registration rather than patient CT, with similar results [24].

First brain images of the NeuroLF system have been presented at the European Conference on Clinical Neuroimaging (ECCN) and the results in comparison to conventional PET/CT devices, even the high-end Biograph Vision Quadra from Siemens (performance characteristics published [25]), have shown non-inferiority [26]

2.2. CareMiBrain

Another recent FDA-cleared device available in the United States is CareMiBrain, developed by OncoVision S.A. (Spain) [20,27]. CareMiBrain is a dedicated brain PET scanner with a compact seated design, designed for neurological imaging, with small installation footprint of 1.2 × 2.5 m^2 and lower cost [20]. Detector modules consist of monolithic LYSO crystals (50 ×50 ×15 mm^3), and SiPM array of 12×12 pixels/module, with depth-of-interaction (DOI) availability. It has transaxial and axial FOV of 240 mm and 152 mm respectively and NEMA NU-2 2012 performance characteristics of: radial/tangential/axial spatial resolution FWHM of 1.87/1.68/1.39 mm and 1.86/1.91/1.40 mm at 1cm and 10 cm [27].

3. Key Findings: Clinical Utility of Compact Standalone Brain PET Systems in AD

The quality of PET images is a critical determinant of the fidelity and clinical utility of the modality for visualizing and quantifying subcortical structures implicated in dementia, as well as for detecting cerebral hypometabolism or pathological biomarker aggregation in AD. Consequently, the accuracy and reliability of early AD detection with brain PET imaging depend on several interrelated factors: 1) PET system – encompassing scanner hardware design, and performance specifications, correction and image reconstruction algorithms, and acquisition protocols. 2) Radiotracer characteristics – including tracer selection, in vivo binding affinity, sensitivity, specificity, and kinetic profile. 3) Patient-related factors – such as head motion during acquisition, comorbidities, and compliance with scanning procedures.

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In the following sections, we discuss how system performance and radiotracer characteristics translate into clinical applications for AD, and how these integrate with emerging biomarker-based diagnostic pathways.

3.1. Dedicated Brain PET System Characteristics in Detection of AD Pathology

The clinical relevance of dedicated brain PET performance characteristics in early AD detection becomes clear when considering the size and distribution of the earliest pathological changes. Neuropathological staging of Alzheimer-related changes as described by Braak and Braak [28], together with structural MRI volumetric studies in patients with amnestic mild cognitive impairment (aMCI) [29] have demonstrated that initial amyloid deposition and tau- related neurofibrillary changes occur in subcortical and medial temporal lobe structures, particularly transentorhinal and entorhinal cortex and hippocampal regions; structures that are typically only about 2-4 mm in thickness, with volumes of less than a few cubic centimetres [30,31].

Conventional whole-body PET systems, which typically provide reconstructed spatial resolutions of >4–7 mm FWHM in brain imaging [32,33], are limited in their ability to reliably visualize small brain structures. This limitation results in pronounced partial volume effects leading to signal loss and underestimation of tracer uptake [34], which has further implications in the quantification performance and Standardized Uptake Value Ratio (SUVr) measurement accuracy, as well as in the early detection of AD and MCI due to AD.

In contrast, dedicated brain PET systems, including commercially available devices, can achieve spatial resolutions of <4 mm FWHM, which combined with smaller detector ring diameter and optimized geometry, can result in accurate detection of early pathological changes in small anatomical regions of the brain, translating into potentially earlier stratification of patients for anti-amyloid therapies.

3.2. Radiotracers and Clinical Applications of Brain PET in AD Diagnosis

Clinical guidelines and consensus recommendations support the use of [^{18}F]-FDG PET, amyloid PET, and more recently tau PET in defined diagnostic scenarios AD [35–40].

[^{18}F]-FDG PET is recognised by the European Academy of Nuclear Medicine (EANM) guidelines as a marker of neurodegeneration and progression (N), included in the ATN classification scheme [38,39]. It is highly sensitive for detecting AD-related hypometabolism but lacks specificity, making it complementary to other biomarkers. In clinical practice, FDG PET is frequently applied for the etiological clarification of uncertain cognitive impairment and the differential diagnosis of neurodegenerative syndromes [42]. It is also recommended to support early diagnosis in MCI [43].

Amyloid PET enables in vivo detection of Aβ plaque burden. Three Aβ PET tracers: [^{18}F]-flutemetamol, [^{18}F]-florbetapir and [^{18}F]-florbetaben are approved for clinical use in both the US and Europe [44]. Appropriate indications include unexplained or progressive MCI, atypical or mixed dementia presentations, and early-onset dementia (<65 years) [37]. A normal amyloid PET essentially rules out AD as the underlying etiology in most patients with cognitive symptoms, whereas a positive scan increases diagnostic certainty but requires age-dependent interpretation [45]. Amyloid PET quantification has been standardized through the Centiloid scale which facilitates harmonization across tracers and sites [46–50]. European Medicines Agency (EMA) has recognized the Centiloid unit for measuring brain amyloid levels as a validated measure of global amyloid load in the brain and the Amyloid Imaging to Prevent AD (AMYPAD) consortium (www.amypad.eu) has demonstrated its utility for both diagnosis and early intervention trials [47–49].

Tau PET reflects the distribution of neurofibrillary tangles in the brain, which correlate more closely with clinical severity than amyloid burden [51]. [^{18}F]-flortaucipir (Tauvid) is the first approved diagnostic tau tracer by both the FDA and EMA [52]. German updated S3 guidelines on dementia now recommend tau-PET for clarifying advanced AD-typical tau pathology in diagnostically uncertain cases [53]. Evidence shows that cognitively unimpaired individuals positive for both amyloid and tau PET had increased risk of progression to MCI and dementia within 3–5 years [54].

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Tau PET also demonstrated high specificity for distinguishing AD from other dementias, supporting its use to "rule in" AD in patients with cognitive impairment at older ages [55]. Efforts are ongoing to standardize tau PET quantification using frameworks analogous to Centiloid [55].

In conclusion, [^{18}F]-FDG, amyloid, and tau PET tracers together form a complementary imaging toolbox, each contributing distinct diagnostic and prognostic value which enhance the clinical utility of dedicated brain PET as an accessible tool in biomarker-driven AD care pathways, from early detection to differential diagnosis and patient stratification for targeted therapies.

3.3. Brain PET in Emerging Diagnostic Workflows of AD

Modern diagnostic criteria increasingly adopt multimodal biomarker frameworks [8–10]. While Aβ and tau can be measured in CSF, comparisons between PET- and CSF-derived measures have revealed subtle but clinically relevant differences, underscoring the added value of combining PET with other modalities to improve specificity in uncertain cases [16].

More recently, plasma-based biomarkers, including Aβ42/Aβ40 ratios and phosphorylated tau (p-tau) isoforms, have emerged as cost-effective and scalable tools to accelerate the diagnostic work-up of AD [16]. At the Alzheimer's Association International Conference (AAIC) 2025 (https://aaic.alz.org),the first in a series of clinical practice guidelines on the use of blood-based biomarkers (BBMs) to assess levels of AD pathology as part of a full diagnostic workup of patients with cognitive impairment presenting to specialized care settings [56]. Importantly, it was emphasised that BBMs should only be used in patients with cognitive impairment for whom AD is a possible diagnosis. The guideline's key recommendations included: (1) BBM tests with ≥90% sensitivity and ≥75% specificity can be used as a triaging test and (2) BBM tests with ≥90% sensitivity and specificity can serve as a substitute for amyloid PET imaging or CSF AD biomarker testing in patients with cognitive impairment presenting to specialized care for memory disorders. Importantly, the panel highlights that there is significant variability in currently available diagnostic test accuracy that many commercially available BBM tests do not meet, hence, cautioned against replacing comprehensive clinical evaluation with BBMs alone [56].

In conclusion, refinements such as biomarker ratios, multimodal combinations, and multi-threshold strategies are expected to improve BBM accuracy. With the approval of DMTs, demand for earlier screening will likely increase, initiating new care pathways that begin in primary care with BBM testing, followed by referral to specialists for confirmatory imaging or treatment initiation [57].

In this evolving workflow, PET will remain the gold standard for confirmatory diagnosis in specialized care, where diagnostic certainty is critical for treatment decisions, clinical trial enrollment, and therapy monitoring [42]. Dedicated brain PET systems, with their lower cost, smaller footprint, and high performance, are uniquely positioned to support this shift by enabling broader access to confirmatory molecular imaging in routine clinical practice.

4. Discussion on Challenges of Access and Cost

Despite its proven technical and clinical value, PET imaging has not yet been widely integrated into the routine diagnostic work-up of AD. Barriers to implementation are multifactorial and differ by healthcare system, encompassing radiotracer availability and cost, lack of standardized diagnostic workflows, restrictive reimbursement policies, and uncertainties regarding the health-economic benefit of early diagnosis. Furthermore, limited geographical distribution of PET scanners constrains access primarily to academic centers or specialized institutions, leaving many neurologists and psychiatrists without established referral pathways. This perpetuates a cycle of low clinical demand and limited investment in new PET capacity [42].

The Neuroimaging Working Group of the German Society of Nuclear Medicine conducted the first nationwide survey on neuro-PET in 2023 [42]. It revealed that 74% of practices were not performing FDG PET and 78% were not performing amyloid PET, largely because 70% of respondents lacked access to a PET scanner. Similarly, a 2023 report from Canada's Drug Agency highlighted that health system readiness for anti-amyloid therapies is compromised by limited PET

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capacity and the logistical challenges of establishing new PET units [57]. Demand for PET scans was observed to increase nearly fourfold within five years after approval of DMTs [57], underscoring the urgency of expanding capacity.

Dedicated brain PET technology offers a potential solution to these bottlenecks. By reducing scanner size, cost, and infrastructure requirements, such systems could expand PET access beyond tertiary referral centers to smaller hospitals and outpatient practices. Cost-effectiveness analyses support this direction: in the U.S., Silverman et al. demonstrated that FDG PET added valuable diagnostic information without increasing overall evaluation and management costs [58], while in Europe, Moulin-Romsee et al. reported substantial healthcare savings and improved patient outcomes when FDG PET was incorporated into the diagnostic work-up of early AD [59].

Future multicentre cohort studies are needed to extend these evaluations to newer biomarkers, such as amyloid and tau PET, and to assess their cost-effectiveness in real-world diagnostic pathways. Such evidence will be essential for establishing reimbursement policies, harmonizing practice guidelines, and ensuring equitable access to brain PET imaging in the era of biomarker-driven AD care.

5. Conclusion

The socio-economic impact of AD is enormous, and the challenge will intensify given the projected rise in prevalence of individuals with this condition [60]. Early and accurate diagnosis of AD is critical to enable interventions at the most effective stage, yet awareness and infrastructure for early intervention remain limited across the EU [6]. With the approval of DMTs, the demand for reliable confirmation of MCI due to AD and early AD will grow, placing additional pressure on healthcare systems to deliver cost-effective diagnostic capacity.

BBMs have recently been recommended as triage or diagnostic tools in patients with cognitive impairment, but variability in diagnostic accuracy and the complexity of AD pathology necessitate confirmatory testing with established modalities. PET remains the gold standard for confirming pathology and for monitoring treatment response in both clinical practice and research.

Dedicated brain PET systems represent a paradigm shift in neuroimaging by offering compact, lower-cost solutions with non-inferior image quality compared to whole-body PET. Their portability and reduced infrastructure requirements could extend PET beyond tertiary centers into neurology and memory clinics, enabling point-of-care confirmation of AD pathology, stratification of patients for anti-amyloid therapies, and treatment monitoring.

Standardization initiatives such as the Centiloid scale for amyloid PET and CenTauR/unitau for tau PET are essential to harmonize quantitative imaging and support widespread adoption.

In parallel, artificial intelligence (AI) is rapidly advancing PET neuroimaging, enabling denoising, reconstruction, attenuation correction, tracer quantification, and automated biomarker classification [61–67]. Emerging AI-driven tools, such as AmyloidPETNet, highlight the feasibility of accurate, fully automated amyloid status determination, while multi-omics models integrating PET with genetic, proteomic, and fluid biomarkers are advancing toward personalized prognosis and treatment response prediction [68,69]. Machine learning approaches for dynamic PET and parametric imaging further illustrate the transformative potential of data-driven quantification [70].

In summary, dedicated brain PET is poised to evolve from a highly specialized, resource-intensive modality into a routine pillar of AD care. Its successful clinical adoption will depend not only on technological innovation, but also on improved access to radiotracers, harmonized standards, reimbursement pathways, clinician education, and robust clinical validation.

When combined with BBMs, advanced analytics, and DMTs, brain PET has the potential to redefine the early diagnosis and management of AD in the coming decade.

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