HSR (LONDON),
HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

# NEUROIMAGING IN THE DIAGNOSIS OF ALZHEIMER'S DISEASE: FROM STRUCTURAL MRI TO MOLECULAR IMAGING AND THE BIOLOGICAL AT(N) FRAMEWORK

**Madjidova Y. N.[1], Radjapov A. A.[1], Shakhabiddinov T. T.[1]**
[1] Neurology, child neurology and medical genetics, TSMU, Tashkent, Uzbekistan
Doi: https://doi.org/10.5281/zenodo.21454075

**Abstract:** Neuroimaging has become an indispensable component of the diagnostic pathway in Alzheimer's disease (AD), a condition increasingly defined by its underlying biology rather than by clinical syndrome alone. Structural magnetic resonance imaging (MRI) remains the first-line modality: it excludes surgically relevant or potentially reversible causes of cognitive decline, characterises the pattern of medial temporal and posterior cortical atrophy, and quantifies the vascular burden that frequently coexists with AD. Standardised visual rating scales—including the medial temporal atrophy (Scheltens) scale, the Koedam posterior atrophy scale, and the Fazekas scale for white-matter change—improve the reproducibility of these assessments, while automated morphometry and machine-learning tools are expanding the precision and scalability of image analysis. Molecular and functional imaging, chiefly [18F]fluorodeoxyglucose, amyloid, and tau positron emission tomography (PET), enables the pathological hallmarks of AD to be detected in vivo, often years before overt atrophy appears. In parallel, cerebrospinal fluid and, more recently, accurate plasma biomarkers such as phosphorylated tau 217 have transformed access to biological confirmation. These advances underpin a shift from syndromic to biological diagnostic criteria, from the 2011 National Institute on Aging–Alzheimer's Association recommendations and the International Working Group criteria to the AT(N) system and the 2024 revised criteria. This review synthesises the contemporary evidence on structural, functional, and molecular neuroimaging in AD, integrates it with fluid biomarkers and current diagnostic frameworks, and outlines a practical, imaging-anchored diagnostic approach together with its limitations and future directions.

**Keywords:** Alzheimer's disease; neuroimaging; magnetic resonance imaging; amyloid PET; tau PET; biomarkers; AT(N); diagnostic criteria.

## 1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia worldwide and imposes a growing burden on patients, families, and health-care systems. For most of its history, the diagnosis rested on clinical criteria supplemented by the exclusion of alternative causes, with definitive confirmation reserved for post-mortem examination. Over the past two decades this paradigm has changed fundamentally. The recognition that a stereotyped sequence of molecular events—β-amyloid accumulation followed by tau-related neurodegeneration—precedes symptom onset by many years has driven a reconceptualisation of AD as a biological continuum that can be detected in living individuals through biomarkers [1,2].

The clinical stakes of accurate diagnosis have risen sharply with the arrival of disease-modifying therapies. Monoclonal antibodies that clear β-amyloid have, for the first time, demonstrated a slowing of clinical decline in early AD, but they require confirmation of amyloid pathology before treatment

HSR (LONDON),
HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

and carry risks that must be monitored by imaging [1,18,19]. In this context, the ability to establish—or exclude—AD biology in vivo, to stage the disease, and to detect treatment-related complications has moved from academic interest to everyday clinical necessity, and neuroimaging is central to each of these tasks.

Conceptually, the biological model of AD rests on a temporally ordered sequence in which β-amyloid accumulation is followed by the spread of neurofibrillary tau pathology, synaptic and neuronal loss, and, ultimately, cognitive decline. Different biomarkers become abnormal at different points along this trajectory, which is why no single modality suffices: amyloid markers change earliest, tau markers track the emergence and progression of symptoms more closely, and markers of neurodegeneration—including MRI atrophy and FDG-PET hypometabolism—capture the downstream injury that most directly parallels clinical severity [2]. Neuroimaging and fluid biomarkers are therefore best understood as complementary readouts of a single evolving process rather than as competing tests.

Neuroimaging sits at the centre of this transformation. It performs two complementary functions. First, structural imaging remains essential for excluding conditions that mimic or contribute to cognitive impairment and for characterising the topography of neurodegeneration. Second, molecular imaging allows the defining proteinopathies of AD to be visualised directly, providing pathological specificity that clinical assessment alone cannot achieve. Together with cerebrospinal fluid (CSF) and blood-based biomarkers, imaging has enabled diagnostic frameworks that separate the biological definition of the disease from its clinical expression [1,3].

The purpose of this review is to provide an integrated account of the role of neuroimaging in the diagnosis of AD. We first consider structural imaging and the visual rating scales and quantitative tools used to interpret it. We then examine functional and molecular imaging, including glucose-metabolism, amyloid, and tau PET, and the monitoring of amyloid-targeting therapies. Finally, we situate imaging within the fluid-biomarker landscape and the evolving diagnostic criteria, propose a practical diagnostic approach, and discuss the principal limitations and future directions of the field.

## 2. Structural neuroimaging

### 2.1. Magnetic resonance imaging as the first-line modality

MRI is the reference structural technique in the assessment of cognitive impairment. Compared with computed tomography (CT), it offers substantially greater soft-tissue contrast and permits detailed evaluation of the medial temporal structures that are affected early in AD [4]. In routine practice, MRI serves several objectives simultaneously: it excludes intracranial mass lesions, chronic subdural collections, and hydrocephalus; it demonstrates the extent and distribution of cerebral atrophy; and it reveals coexisting vascular and other pathologies that influence the clinical picture and prognosis. The most characteristic structural features of AD are atrophy of the hippocampus and entorhinal cortex, widening of the temporal horns of the lateral ventricles, parietal atrophy, and, in later stages, generalised cortical atrophy. Importantly, the absence of prominent atrophy does not exclude early disease, particularly when supportive biomarkers are positive [4].

### 2.2. Recommended MRI protocol

A standardised protocol maximises the diagnostic yield of MRI in suspected AD and ensures that both neurodegenerative and vascular contributions are captured (Table 1). High-resolution three-

HSR (LONDON),
HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

dimensional T1-weighted acquisition provides the anatomical detail required for visual and automated volumetric assessment of atrophy. T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences depict structural lesions and white-matter change, diffusion-weighted imaging identifies acute ischaemia and is valuable in rapidly progressive dementia, and susceptibility-sensitive sequences reveal microhaemorrhages. This combination allows the reader to assess atrophy while simultaneously evaluating small-vessel disease, lacunar infarcts, microbleeds, and other conditions capable of affecting cognition.

**Table 1.** Recommended MRI protocol for the assessment of suspected Alzheimer's disease.

| Sequence | Primary purpose |
|---|---|
| 3D T1-weighted (high resolution) | Volumetric assessment of hippocampal and cortical atrophy; input for automated morphometry |
| T2-weighted | Detection of structural lesions and comorbid pathology |
| FLAIR | White-matter hyperintensities, lacunes, periventricular change |
| Diffusion-weighted imaging (DWI) | Acute ischaemia; rapidly progressive dementia (e.g., prion disease) |
| SWI or T2*-GRE | Cerebral microbleeds, superficial siderosis, calcification; baseline before anti-amyloid therapy |
| MR angiography (optional) | Large-vessel assessment when clinically indicated |

### 2.3. Medial temporal atrophy and the Scheltens (MTA) scale

The hippocampus is among the earliest structures affected in AD, and morphometric studies show that its volume begins to decline several years before clinical symptoms emerge [4]. On MRI, the relevant assessment includes hippocampal volume, the width of the choroidal fissure, the size of the temporal horn of the lateral ventricle, and the state of the parahippocampal gyrus. The severity of hippocampal atrophy correlates closely with impairment of episodic memory and has prognostic value for progression from mild cognitive impairment (MCI) to dementia.

To standardise this evaluation, the medial temporal atrophy (MTA) scale proposed by Scheltens is widely used [5]. The scale rates each hemisphere separately on a five-point scale from 0 (no atrophy) to 4 (severe atrophy), based on the width of the choroidal fissure and temporal horn and the height of the hippocampal formation (Table 2). Interpretation must be age-adjusted, because a modest reduction in hippocampal volume can occur with physiological ageing; commonly applied thresholds regard a score of 2 or more as abnormal below the age of 75 years and 3 or more at older ages. High MTA scores substantially increase the likelihood of AD, especially in the presence of a compatible clinical picture.

Longitudinal measurement adds a temporal dimension to these cross-sectional ratings. Annualised rates of hippocampal and whole-brain atrophy are among the most sensitive structural markers of neurodegeneration and are widely used as outcome measures in therapeutic trials [4]. At the tissue level, atrophy in AD preferentially involves the CA1 and subiculum hippocampal subfields and the entorhinal cortex, mirroring the early sites of neurofibrillary pathology. Because visual rating

HSR (LONDON),
HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

and manual measurement are influenced by reader experience and head positioning, harmonised acquisition and, increasingly, automated segmentation are recommended to improve reliability, particularly when serial comparison is intended [4].

### 2.4. Posterior atrophy and the Koedam scale

Beyond the medial temporal region, AD involves the parietal lobes, with the inferior parietal lobule, precuneus, posterior cingulate, and parietal association cortex among the most affected areas. These changes are particularly prominent in atypical, early-onset presentations, including posterior cortical atrophy. The Koedam posterior atrophy scale grades parieto-occipital, precuneus, and posterior cingulate atrophy on a four-point scale (0–3) and is especially useful in younger patients and when posterior cortical atrophy is suspected [6]. Combined use of the MTA and Koedam scales provides a more complete morphological profile than either alone (Table 2).

### 2.5. Vascular changes and the Fazekas scale

A substantial proportion of patients with AD have concurrent cerebrovascular changes, including leukoaraiosis, lacunar infarcts, microinfarcts, microbleeds, and enlarged perivascular spaces. Such changes can aggravate the cognitive deficit and influence prognosis, and their identification allows vascular risk factors to be addressed. The Fazekas scale grades white-matter hyperintensities into three degrees—from small focal changes (grade 1) through early confluent change (grade 2) to extensive confluent involvement (grade 3) [7]. Higher grades indicate a significant vascular contribution to cognitive impairment and should prompt comprehensive assessment in conjunction with clinical and other imaging data (Table 2).

**Table 2.** Visual rating scales commonly used in the structural work-up of Alzheimer's disease.

| Scale | Region assessed | Range | Interpretation notes |
|---|---|---|---|
| MTA (Scheltens) | Medial temporal lobe / hippocampus | 0–4 per hemisphere | Age-adjusted thresholds (e.g., ≥2 if <75 y; ≥3 if ≥75 y) |
| Koedam (posterior atrophy) | Parieto-occipital, precuneus, posterior cingulate | 0–3 | Useful in early-onset AD and posterior cortical atrophy |
| Fazekas | White-matter hyperintensities | 1–3 | Grades small-vessel burden; higher grades = greater vascular contribution |

### 2.6. Microbleeds, susceptibility-weighted imaging, and ARIA

Susceptibility-weighted imaging (SWI) and T2*-gradient-echo sequences are sensitive to paramagnetic products and detect cerebral microbleeds, superficial siderosis, calcification, and vascular malformations [8]. Cerebral microbleeds are increasingly recognised across the spectrum of ageing and are particularly frequent in AD and cerebral amyloid angiopathy. Their assessment has acquired additional importance with the advent of anti-amyloid immunotherapy: baseline microbleed burden and superficial siderosis are among the factors that inform eligibility and risk, and susceptibility-sensitive sequences are central to detecting the haemorrhagic form of amyloid-related imaging abnormalities (ARIA-H) during treatment [8,17].

HSR (LONDON),
HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

### 2.7. Computed tomography

CT is used chiefly when MRI cannot be performed—for example, in the presence of contraindications, in the emergency setting, or when acute intracranial processes are suspected. It can demonstrate marked atrophy, hydrocephalus, tumours, large infarcts, and intracranial haemorrhage. However, its sensitivity to the early changes of AD is considerably lower than that of MRI, and it does not reliably resolve the medial temporal structures that are diagnostically informative (Table 4).

### 2.8. Automated quantitative morphometry

Contemporary software enables automated calculation of the volumes of individual brain structures, including the hippocampus and amygdala, cortical thickness, ventricular volume, and total grey- and white-matter volume. Compared with visual rating, quantitative morphometry improves reproducibility and provides continuous measures that are well suited to tracking change over serial examinations. Whole-brain and hippocampal atrophy rates are sufficiently sensitive to serve as outcome measures in disease-modifying trials, and normative comparison can support the interpretation of borderline cases [4]. Standardisation of acquisition and analysis remains essential to ensure that quantitative outputs are comparable across scanners and centres.

### 2.9. Artificial intelligence in the analysis of MRI

Machine-learning and deep-learning methods have substantially extended the analysis of neuroimaging data. Algorithms can automatically segment brain structures, detect subtle atrophy, classify diagnostic groups, and estimate the risk of progression from MCI to dementia, and they can process large image datasets efficiently [9]. Conventional approaches such as support vector machines and random forests, together with convolutional neural networks and more recent architectures, have achieved high classification accuracy in research settings [9]. Nonetheless, these systems are best regarded as decision-support tools rather than replacements for expert clinical assessment. Their deployment requires independent clinical validation, transparency of the underlying algorithms, attention to pitfalls such as class imbalance and data leakage, and compliance with the regulatory requirements applicable to medical software.

### 2.10. Imaging patterns across the clinical variants of Alzheimer's disease

Although the amnestic presentation with medial temporal atrophy is the most common, AD is heterogeneous, and its atypical variants have distinctive imaging correlates. Posterior cortical atrophy, the visual variant, is characterised by prominent parieto-occipital and precuneus atrophy that the Koedam scale is well suited to capture, often with relatively preserved medial temporal structures [6]. The logopenic variant of primary progressive aphasia typically shows left temporoparietal atrophy and hypometabolism, whereas a dysexecutive or behavioural presentation may display greater frontal and parietal involvement. Recognition of these patterns matters because medial temporal atrophy can be mild or absent in younger patients and in atypical phenotypes, in which posterior atrophy scores and molecular imaging carry proportionally greater diagnostic weight [3,6].

## 3. Functional and molecular neuroimaging

Whereas structural MRI and CT depict anatomical change, functional and molecular imaging interrogate pathophysiological processes in vivo, frequently before pronounced atrophy develops. The principal techniques are positron emission tomography (PET) with [18F]fluorodeoxyglucose (FDG),

HSR (LONDON),
HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

amyloid PET, tau PET, and single-photon emission computed tomography (SPECT). Each reflects a distinct aspect of AD pathogenesis and carries its own indications, strengths, and limitations.

### 3.1. Principles of positron emission tomography

PET is based on the detection of gamma photons generated by the annihilation of positrons emitted by a radiotracer. After intravenous administration, the labelled compound accumulates in tissue in proportion to the physiological or pathological process under study. In neurology, PET can assess cerebral glucose metabolism, the distribution of β-amyloid, the accumulation of pathological tau, and, in specialised research, the activity of individual neurotransmitter systems. A principal advantage of the method is its sensitivity to early changes that precede structural atrophy.

### 3.2. FDG-PET

FDG-PET uses [18F]fluorodeoxyglucose, a glucose analogue whose uptake reflects tissue metabolic activity. Because neurons depend heavily on glucose, reduced uptake indicates impaired functional activity of the corresponding regions. In AD, the characteristic pattern comprises bilateral temporoparietal hypometabolism, reduced metabolism in the posterior cingulate and precuneus, and relative preservation of primary sensorimotor cortices in the early stages; with progression, hypometabolism extends to the frontal cortex. FDG-PET is particularly informative in diagnostically challenging or atypical cases, in early-onset disease, and in the differential diagnosis of dementias—most notably between AD and frontotemporal degeneration, which display distinct metabolic signatures [3] (Table 3, Table 4).

The specificity of the metabolic topography is diagnostically valuable. Frontotemporal degeneration produces predominantly frontal and anterior temporal hypometabolism, in contrast to the temporoparietal and posterior cingulate pattern of AD, while dementia with Lewy bodies characteristically involves the occipital cortex, often with relative preservation of posterior cingulate metabolism—the so-called cingulate island sign [16]. FDG-PET therefore complements amyloid imaging: whereas amyloid PET establishes the presence of pathology, the metabolic pattern helps to localise dysfunction and to distinguish among neurodegenerative syndromes when the clinical picture is ambiguous [3].

### 3.3. Amyloid PET

Amyloid PET visualises the accumulation of fibrillar β-amyloid in the brain. The first widely used tracer, [11C]Pittsburgh Compound-B, demonstrated in vivo retention in association cortices known to contain amyloid deposits and established the feasibility of imaging amyloid pathology during life [10]. Subsequent [18F]-labelled tracers—florbetapir, florbetaben, and flutemetamol—offered longer half-lives suitable for routine clinical use, and the Centiloid scale was introduced to harmonise quantification across tracers and centres (Table 3). A positive scan indicates significant amyloid pathology but does not by itself establish a clinical diagnosis of AD, because amyloid can be present in cognitively unimpaired older adults [3,10].

Guidance on when amyloid PET is appropriate has been formalised in appropriate-use criteria developed jointly by professional societies [11]. In general, the investigation is recommended when its result is likely to change management: examples include MCI of uncertain aetiology, atypical clinical presentations, early-onset dementia, and the need for biological confirmation before considering disease-modifying therapy. It is not recommended in the setting of a typical late-onset dementia when

HSR (LONDON),
HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

the result would not alter care. Real-world evidence indicates that amyloid PET can change diagnosis and management in a substantial proportion of patients evaluated by dementia specialists [12].

Amyloid PET can be interpreted by binary visual read, following tracer-specific criteria that classify a scan as amyloid-positive or amyloid-negative, or quantitatively using the Centiloid scale, on which values are anchored so that a typical young control approximates zero and a typical patient with AD dementia approximates one hundred. Quantification assists the assessment of borderline scans and the harmonisation of results across tracers and centres. The principal interpretive caveat is that amyloid positivity increases with age among cognitively unimpaired individuals, so a positive scan must always be integrated with the clinical and cognitive context rather than equated with dementia [3,10].

**Table 3.** Principal PET radiotracers used in Alzheimer's disease.

| Category | Representative tracers | Molecular target | Main clinical role |
|---|---|---|---|
| Glucose metabolism | [18F]FDG | Regional cerebral glucose metabolism | Differential diagnosis of dementias |
| Amyloid | [18F]florbetapir, [18F]florbetaben, [18F]flutemetamol, [11C]PiB | Fibrillar β-amyloid | Confirm/exclude amyloid; Centiloid quantification |
| Tau | [18F]flortaucipir; later-generation tracers | Paired helical filament tau | Staging, prognosis, therapy selection |

### 3.4. Tau PET

Tau PET images the deposition of pathological tau, the neurofibrillary component of AD that correlates more closely than amyloid with the topography and severity of cognitive impairment. The tracer [18F]flortaucipir binds with high affinity to paired helical filament tau, shows favourable kinetics, and provides good discriminative accuracy for AD; ante-mortem uptake correlates with post-mortem tau burden [13]. In a structured biomarker-development framework, flortaucipir has satisfied the early requirements for analytical and discriminative validity, whereas evidence for early-detection performance and demonstrable effects on health outcomes continues to accrue [13]. Clinically, the distribution of tau uptake—progressing from temporo-limbic to neocortical regions—offers information on disease stage and prognosis and can increase confidence that AD is contributing to a patient's symptoms; it is also relevant to therapy selection, as tau burden was used to stratify participants in recent immunotherapy trials [13,19] (Table 3).

The spatial pattern of tau-PET signal broadly recapitulates the neuropathological Braak staging of neurofibrillary pathology, spreading from transentorhinal and limbic regions to temporal and finally to widespread neocortical areas, which allows an in-vivo estimate of disease stage that correlates with the severity and profile of cognitive impairment [13]. First-generation tracers such as flortaucipir show off-target binding—for example in the choroid plexus and basal ganglia—that must be recognised during interpretation, and later-generation tracers have been developed to mitigate these limitations.

HSR (LONDON),
HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

Within the 2024 framework, tau PET is a Core 2 biomarker: it is not required to establish the diagnosis but refines prognosis and increases confidence that AD is responsible for a patient's symptoms [1,13].

### 3.5. SPECT and dopamine-transporter imaging

Where PET is unavailable, perfusion SPECT can demonstrate posterior temporoparietal hypoperfusion analogous to the FDG-PET pattern, although with lower spatial resolution. Dopamine-transporter (DAT) SPECT has a specific role in differential diagnosis: markedly reduced striatal DAT uptake supports dementia with Lewy bodies, whereas uptake is typically preserved in AD. DAT imaging is incorporated as an indicative biomarker in the consensus criteria for dementia with Lewy bodies, in which the accurate separation from AD has direct management implications [16] (Table 4).

### 3.6. Monitoring anti-amyloid therapy: amyloid-related imaging abnormalities

The approval of amyloid-lowering monoclonal antibodies has made imaging surveillance an integral part of treatment. Anti-amyloid agents reduce amyloid burden and modestly slow clinical decline, but are associated with amyloid-related imaging abnormalities (ARIA), which comprise a vasogenic-oedema/effusion form (ARIA-E) seen on FLAIR and a haemorrhagic form (ARIA-H) seen on susceptibility-sensitive sequences [17]. In pivotal phase 3 trials of lecanemab and donanemab, ARIA occurred in a clinically important minority of treated participants, underscoring the need for structured MRI monitoring [18,19]. Recommendations for the detection and monitoring of ARIA specify baseline and scheduled follow-up MRI, with FLAIR and SWI/T2*-GRE sequences, and provide a framework for grading severity and guiding management when abnormalities appear [17]. Prompt clinical evaluation and treatment adjustment in accordance with current guidance are required when symptomatic ARIA is identified.

### 3.7. Criteria for the rational use of imaging

Selection among imaging modalities should follow several principles: the investigation should answer a specific clinical question; its result should be capable of changing management; preference should be given to methods with the best balance of diagnostic value, safety, and availability; and interpretation should be undertaken by a multidisciplinary team in the light of clinical and laboratory data. The combined use of structural and molecular imaging brings diagnosis closer to accurate in-vivo characterisation of AD and provides the basis for a personalised approach (Table 4).

**Table 4.** Comparison of the main neuroimaging modalities in Alzheimer's disease.

| Modality | What it measures | Typical AD findings | Principal indications | Key limitations |
|---|---|---|---|---|
| CT | Gross structure | Atrophy; exclusion of mass, haemorrhage, hydrocephalus | MRI contraindicated; emergency | Low sensitivity for early change |
| MRI | Atrophy, vascular change, microbleeds | MTA, posterior atrophy, white-matter disease | First-line structural work-up; ARIA monitoring | Does not directly show molecular pathology |

HSR (LONDON),
HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

| Modality | What it measures | Typical AD findings | Principal indications | Key limitations |
|---|---|---|---|---|
| FDG-PET | Glucose metabolism | Temporoparietal and posterior cingulate hypometabolism | Atypical/early-onset; AD vs FTD | Non-specific; cost/availability |
| Amyloid PET | β-amyloid | Diffuse cortical uptake | Biological confirmation before therapy | May be positive in cognitively normal elders |
| Tau PET | Tau tangles | Temporo-limbic then neocortical uptake | Staging/prognosis; therapy selection | Limited availability; off-target binding |
| SPECT (perfusion / DAT) | Perfusion / dopamine transporter | Posterior hypoperfusion; preserved DAT in AD | PET unavailable; AD vs DLB | Lower resolution than PET |

### 3.8. Advanced and emerging imaging techniques

Beyond the established modalities, several advanced techniques contribute increasingly to research and, in selected settings, to clinical characterisation. Arterial spin labelling provides a non-invasive, contrast-free measure of cerebral perfusion that reproduces the posterior temporoparietal hypoperfusion seen with FDG-PET and SPECT. Resting-state functional MRI has revealed early disruption of the default-mode network in AD, spatially overlapping the regions of amyloid deposition and hypometabolism, and diffusion-tensor imaging detects microstructural white-matter change that may precede macroscopic atrophy. These methods are not yet part of routine diagnostic protocols, but they are informative for understanding disease mechanisms, for enriching clinical trials, and, potentially, for earlier detection as acquisition and analysis mature [2,4].

## 4. Fluid biomarkers as diagnostic context

Imaging is increasingly interpreted alongside fluid biomarkers, and the two are complementary. Established CSF measures—the Ab42/Ab40 ratio and phosphorylated tau—reflect amyloid and tau pathology and have long supported biological diagnosis. The most consequential recent development is the maturation of blood-based biomarkers, in particular plasma phosphorylated tau 217 (p-tau217). In large cohort studies, plasma p-tau217 discriminated AD from other neurodegenerative disorders with accuracy exceeding that of other plasma and MRI markers and approaching that of CSF- and PET-based measures [14]. Commercially available p-tau217 immunoassays have since demonstrated high accuracy for detecting abnormal amyloid and tau pathology, comparable with CSF biomarkers and with reproducible cut-offs across cohorts [15]. Because such assays are more accessible and less invasive than PET or lumbar puncture, they are poised to broaden biological confirmation of AD—

HSR (LONDON),
HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

while still requiring imaging for the exclusion of alternative pathology and for therapy-related monitoring.

A fuller account of the fluid-biomarker landscape helps to situate imaging within contemporary diagnosis. In CSF, a reduced Aβ42/Aβ40 ratio reflects amyloid deposition, while elevated phosphorylated tau (p-tau181 and p-tau217) and total tau indicate tau pathology and neuronal injury, respectively. In blood, in addition to p-tau217, glial fibrillary acidic protein has emerged as an early marker of amyloid-associated astrocytic reactivity, and neurofilament light provides a sensitive but non-specific index of neuroaxonal damage useful for tracking neurodegeneration across disorders. A practical consequence is the emergence of tiered pathways in which an accessible blood test triages patients, reserving PET or CSF analysis for confirmation in selected cases—an approach in which structural MRI retains its role in excluding alternative pathology and guiding therapy [1,14,15].

## 5. Diagnostic criteria and the biological definition of Alzheimer's disease

The interpretation of imaging and fluid biomarkers is framed by successive iterations of diagnostic criteria, which have progressively moved AD from a clinically defined syndrome toward a biologically defined disease.

### 5.1. The 2011 NIA-AA criteria

In 2011, the National Institute on Aging and the Alzheimer's Association revised the earlier 1984 criteria across three stages of disease—preclinical, MCI due to AD, and AD dementia [20,21]. The core clinical criteria remained the cornerstone of diagnosis in practice, but for the first time biomarker evidence was formally incorporated to increase pathophysiological specificity, distinguishing between the disease process and the clinical syndrome it produces [20]. This conceptual separation laid the groundwork for subsequent biological definitions.

### 5.2. The International Working Group criteria

The International Working Group (IWG) has articulated a clinical–biological approach in which the diagnosis of AD is reserved for individuals who have both a specific AD clinical phenotype and supportive biomarker evidence [3]. In response to purely biomarker-based definitions, the IWG has emphasised that cognitively unimpaired individuals with positive biomarkers should be regarded as at risk of progression rather than as having the disease, given that many will not develop clinical manifestations in their lifetime and that AD pathology commonly coexists as a comorbidity in other brain disorders [3]. This position highlights the continuing debate over how biological information should be applied in everyday clinical care.

### 5.3. The AT(N) system

The 2018 NIA-AA Research Framework introduced a biomarker classification, AT(N), that groups markers by the pathological process each measures: A for β-amyloid deposition, T for pathological tau, and N for neurodegeneration [2]. This scheme is deliberately flexible: new biomarkers can be assigned to existing categories, and additional categories can be added as they emerge. AT(N) shifted the research definition of AD in living people from a syndromic to a biological construct and provided a common language for characterising where an individual lies on the disease continuum [2] (Table 5).

HSR (LONDON),
HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

**Table 5.** The AT(N) biomarker classification and its extension in later frameworks.

| Category | Biomarker examples | Interpretation |
|---|---|---|
| A – Amyloid | Amyloid PET; CSF Ab42 or Ab42/40; plasma p-tau217 | Aggregated β-amyloid / AD neuropathologic change |
| T – Tau | CSF phosphorylated tau; tau PET | Phosphorylated (soluble) and aggregated (deposited) tau |
| N – Neurodegeneration | MRI atrophy; FDG-PET; neurofilament light | Non-specific neuronal injury / neurodegeneration |
| Extended markers | Inflammatory and vascular markers (e.g., GFAP) | Copathology and disease modifiers |

### 5.4. The 2024 revised criteria

The 2024 revised criteria of the Alzheimer's Association Workgroup formalise the biological definition of AD, defining the disease as a process that begins with AD neuropathologic change while individuals are asymptomatic and progresses to later clinical symptoms [1]. The framework distinguishes early-changing Core 1 biomarkers—amyloid PET, approved CSF markers, and accurate plasma markers, especially p-tau217—which map onto the amyloid or AD-tauopathy pathways and reflect AD neuropathologic change more generally; an abnormal Core 1 result is considered sufficient to establish a diagnosis of AD [1]. Later-changing Core 2 biomarkers, including tau PET, provide prognostic information and, when abnormal, increase confidence that AD is contributing to symptoms. An integrated biological and clinical staging scheme accommodates the fact that copathology, cognitive reserve, and resistance can modify the relationship between biological and clinical stages [1]. Within this scheme, structural MRI contributes principally to the N category and to the exclusion of alternative and contributory pathology, while amyloid and tau PET populate the A and T categories.

The 2024 framework also elaborates staging. Alongside the traditional syndromic categories of cognitively unimpaired, MCI, and dementia, it incorporates a biological staging of biomarker burden and an integrated clinical–biological staging that acknowledges discordance between the two. Because copathology, cognitive reserve, and resilience can decouple the biological stage from the clinical stage, some individuals present with clinical impairment more advanced than their biological stage would predict, while others show the reverse. This explicit accommodation of discordance is one of the framework's principal advances and has direct implications for prognosis and for the interpretation of a patient's imaging and fluid biomarkers [1].

### 5.5. Preclinical Alzheimer's disease and MCI due to AD

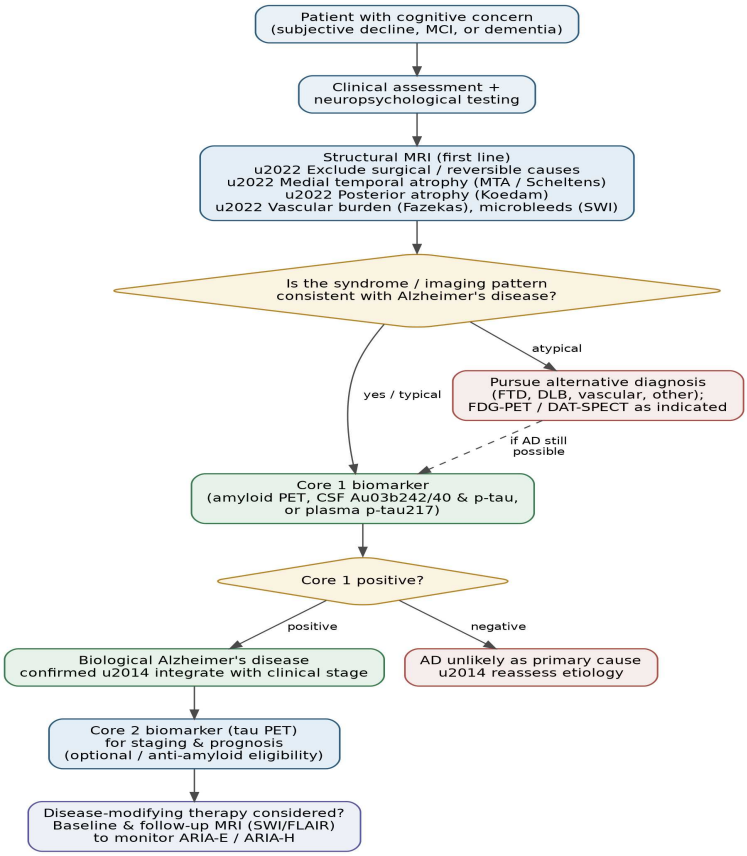
The biological framework accommodates a preclinical stage, in which biomarker evidence of AD pathology is present in cognitively unimpaired individuals, and a prodromal stage of MCI due to AD, in which subtle cognitive impairment coexists with supportive biomarkers [2,20]. Imaging contributes to both: amyloid and tau PET can detect pathology before symptom onset, and structural and quantitative MRI can document early neurodegeneration and predict progression. The clinical use of these stages must be tempered by the recognition, emphasised by the IWG, that biomarker positivity in the absence of a compatible phenotype denotes risk rather than established disease [3].

HSR (LONDON),
HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

### 6. An integrated, imaging-anchored diagnostic approach

In practice, the evaluation of a patient with cognitive concern proceeds from clinical and neuropsychological assessment to structural MRI, which excludes surgically relevant or reversible causes and characterises the pattern and severity of atrophy and vascular burden using the scales described above. When the syndrome and imaging pattern are compatible with AD, a Core 1 biomarker—amyloid PET, CSF, or plasma p-tau217—is used to confirm or exclude the biology; when the presentation is atypical, FDG-PET and, where relevant, DAT-SPECT help to identify alternative diagnoses. Confirmation of biological AD is then integrated with the clinical stage, and Core 2 biomarkers such as tau PET may be added for staging, prognosis, and therapy selection. If disease-modifying treatment is contemplated, baseline and scheduled follow-up MRI with FLAIR and susceptibility-sensitive sequences are required to monitor for ARIA. This sequence is summarised in Figure 1.

Several practical principles govern this pathway. Investigations should be ordered to answer a specific question whose answer could change management, avoiding indiscriminate testing; results should be interpreted by a multidisciplinary team that integrates clinical, neuropsychological, imaging, and laboratory data; and the least invasive, most available modality capable of resolving the question should be preferred. Where accurate blood-based markers are available, they can serve as an efficient first step, with PET or CSF reserved for confirmation or for resolving discordant findings. Throughout, structural MRI remains foundational—both for excluding contributory or alternative pathology and, once therapy is contemplated, for establishing the baseline against which treatment-related changes are judged.



HSR (LONDON),
HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

**Figure 1.** Integrated, imaging-anchored diagnostic pathway for Alzheimer's disease, from clinical assessment and structural MRI through Core 1 and Core 2 biomarkers to therapy-related monitoring. MCI, mild cognitive impairment; MTA, medial temporal atrophy; SWI, susceptibility-weighted imaging; FTD, frontotemporal dementia; DLB, dementia with Lewy bodies; ARIA, amyloid-related imaging abnormalities.

## 7. Limitations and future directions

Despite substantial progress, important limitations remain. Molecular imaging is costly and unevenly available, and its interpretation must account for the presence of amyloid pathology in some cognitively normal older adults and for off-target tracer binding. Quantitative and machine-learning tools require rigorous standardisation of acquisition and analysis, external validation in diverse and unselected populations, algorithmic transparency, and appropriate regulatory oversight before wide clinical adoption [9]. Copathology—vascular disease, Lewy-body pathology, and TDP-43—frequently coexists with AD and complicates both imaging interpretation and the mapping between biological and clinical stages [1,3]. Incidental findings on structural imaging must be managed judiciously, and the equitable deployment of biomarker-based diagnosis across health systems with differing resources is a pressing concern.

Access and equity deserve particular emphasis. PET and CSF testing are concentrated in specialist centres, and the geographical and economic distribution of these resources is uneven; validation of biomarkers in diverse populations, including groups under-represented in the cohorts on which current thresholds were derived, remains incomplete [3]. The interpretation of quantitative imaging is sensitive to scanner hardware, field strength, and analysis pipelines, so that cut-offs established in one setting may not transfer directly to another. Finally, the communication of biomarker results—especially in cognitively unimpaired individuals in whom positivity denotes risk rather than disease—raises ethical and practical challenges that clinical services must be prepared to address [3].

Future directions include the continued integration of accessible blood-based biomarkers with imaging to create tiered diagnostic pathways, the refinement and clinical validation of tau PET for staging and treatment selection, the maturation of automated and artificial-intelligence tools within regulated clinical workflows, and the harmonisation of quantitative imaging through scales such as Centiloid. As disease-modifying therapies enter practice, imaging will remain central not only to diagnosis and staging but also to the safe delivery and monitoring of treatment [17,18,19].

## 8. Conclusion

Structural neuroimaging remains a mandatory step in the assessment of every patient with suspected Alzheimer's disease: correct interpretation of MRI confirms characteristic atrophy patterns, reveals mixed dementias, excludes potentially reversible causes of cognitive decline, and informs the safety and prospects of disease-modifying therapy. Molecular imaging adds pathological specificity by depicting amyloid and tau in vivo, and, together with CSF and plasma biomarkers, underpins the contemporary biological definition of the disease embodied in the AT(N) system and the 2024 revised criteria. In combination with clinical evaluation, neuropsychological testing, and fluid biomarkers, neuroimaging forms the foundation of accurate, in-vivo, and increasingly personalised diagnosis of Alzheimer's disease.

HSR (LONDON),
HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

**Declarations**

**Funding:** [to be completed].

**Conflicts of interest:** [to be completed].

**Author contributions:** [to be completed].

**Data availability:** Not applicable (narrative review).

## References

1. Jack CR Jr, Andrews JS, Beach TG, Buracchio T, Dunn B, Graf A, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimers Dement. 2024;20(8):5143–5169. doi:10.1002/alz.13859
2. Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018;14(4):535–562. doi:10.1016/j.jalz.2018.02.018
3. Dubois B, Villain N, Frisoni GB, Rabinovici GD, Sabbagh M, Cappa S, et al. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. Lancet Neurol. 2021;20(6):484–496. doi:10.1016/S1474-4422(21)00066-1
4. Frisoni GB, Fox NC, Jack CR Jr, Scheltens P, Thompson PM. The clinical use of structural MRI in Alzheimer disease. Nat Rev Neurol. 2010;6(2):67–77. doi:10.1038/nrneurol.2009.215
5. Scheltens P, Leys D, Barkhof F, Huglo D, Weinstein HC, Vermersch P, et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry. 1992;55(10):967–972. doi:10.1136/jnnp.55.10.967
6. Koedam ELGE, Lehmann M, van der Flier WM, Scheltens P, Pijnenburg YAL, Fox N, et al. Visual assessment of posterior atrophy: development of a MRI rating scale. Eur Radiol. 2011;21(12):2618–2625. doi:10.1007/s00330-011-2205-4
7. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol. 1987;149(2):351–356. doi:10.2214/ajr.149.2.351
8. Haller S, Vernooij MW, Kuijer JPA, Larsson E-M, Jäger HR, Barkhof F. Cerebral microbleeds: imaging and clinical significance. Radiology. 2018;287(1):11–28. doi:10.1148/radiol.2018170803
9. Zhao Z, Chuah JH, Lai KW, Chow C-O, Gochoo M, Dhanalakshmi S, et al. Conventional machine learning and deep learning in Alzheimer's disease diagnosis using neuroimaging: a review. Front Comput Neurosci. 2023;17:1038636. doi:10.3389/fncom.2023.1038636
10. Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol. 2004;55(3):306–319. doi:10.1002/ana.20009
11. Johnson KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Herscovitch P, et al. Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. Alzheimers Dement. 2013;9(1):e1–e16. doi:10.1016/j.jalz.2013.01.002

HSR (LONDON),
HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

12. Rabinovici GD, Gatsonis C, Apgar C, Chaudhary K, Gareen I, Hanna L, et al. Association of amyloid positron emission tomography with subsequent change in clinical management among Medicare beneficiaries with mild cognitive impairment or dementia. JAMA. 2019;321(13):1286–1294. doi:10.1001/jama.2019.2000
13. Wolters EE, Dodich A, Boccardi M, Corre J, Drzezga A, Hansson O, et al. Clinical validity of increased cortical uptake of [18F]flortaucipir on PET as a biomarker for Alzheimer's disease in the context of a structured 5-phase biomarker development framework. Eur J Nucl Med Mol Imaging. 2021;48(7):2097–2109. doi:10.1007/s00259-020-05118-w
14. Palmqvist S, Janelidze S, Quiroz YT, Zetterberg H, Lopera F, Stomrud E, et al. Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders. JAMA. 2020;324(8):772–781. doi:10.1001/jama.2020.12134
15. Ashton NJ, Brum WS, Di Molfetta G, Benedet AL, Arslan B, Jonaitis E, et al. Diagnostic accuracy of a plasma phosphorylated tau 217 immunoassay for Alzheimer disease pathology. JAMA Neurol. 2024;81(3):255–263. doi:10.1001/jamaneurol.2023.5319
16. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor J-P, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. Neurology. 2017;89(1):88–100. doi:10.1212/WNL.0000000000004058
17. Sperling RA, Jack CR Jr, Black SE, Frosch MP, Greenberg SM, Hyman BT, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup. Alzheimers Dement. 2011;7(4):367–385. doi:10.1016/j.jalz.2011.05.2351
18. van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in early Alzheimer's disease. N Engl J Med. 2023;388(1):9–21. doi:10.1056/NEJMoa2212948
19. Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, et al. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. JAMA. 2023;330(6):512–527. doi:10.1001/jama.2023.13239
20. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):263–269. doi:10.1016/j.jalz.2011.03.005
21. Jack CR Jr, Albert MS, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, et al. Introduction to the recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):257–262. doi:10.1016/j.jalz.2011.03.004