IMJ
Official Journal of the Irish Medical Organisation

Ir Med J; November-December 2024; Vol 117; No. 10; P1063

December 19th, 2024

The Use of Biomarkers in Diagnosing Alzheimer's Disease: Recommendations of the Irish Working Group on Biological Approaches to the Diagnosis of Dementia

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Introduction

Alzheimer's disease (AD) and dementia represent a looming crisis for Irish society: the prevalence of dementia nationwide is expected to double by the year 2045[1]. This will inevitably lead to a growing number of patients presenting with cognitive decline. The initial assessment of a patient with cognitive concerns most often begins in primary care. It involves taking a detailed clinical history from the patient and ideally an informant, focusing on multi-domain cognitive performance and impact on function[1]. Potentially reversible contributors to cognitive impairment e.g. medications, depression or sleep disorders should be considered. A clinical examination and cognitive tests are performed. Routine blood tests include full blood count, renal, liver and bone profile, glucose, vitamin B12, thyroid function tests, and syphilis and HIV serology in certain cases[1]. Structural imaging plays a central role in the evaluation of cognitive concerns: MRI brain scans detect regional atrophy, assess the burden of vascular disease and rule-out structural mimics[2]. If appropriate, onward referral to specialists in Memory Assessment and Support Services (MASS), Regional Specialist Memory Clinics (RSMC) or Cognitive/Behavioural Neurology services for further clinical review, multidisciplinary assessments and diagnostic tests occurs.

The diagnostic pathway for AD has transformed with the advent of AD-specific cerebrospinal fluid (CSF) and imaging biomarkers. This reflects the evolution of AD diagnostic criteria: from a pure clinical diagnosis[3]; to incorporating biomarkers on a research basis[4-9]; and most recently integrating both clinical and biological data in the revised 'International Working Group' (IWG)[10] and 'National Institute on Ageing and the Alzheimer's Association' (NIA-AA)[2] diagnostic criteria. In those diagnosed with AD, clinical staging depends on the degree of cognitive and functional impairment (Table 1) [2]. The pattern of cognitive decline most commonly seen in AD is progressive amnestic dysfunction that evolves over-time into multi-domain dementia. However, there are also non-amnestic or "atypical" presentations characterised by symptom onset with predominant dysfunction in visual (posterior cortical atrophy (PCA)[11]), language (logopenic variant primary progressive aphasia (lvPPA)), frontal (behavioural/dysexecutive[12]) or motor domains (corticobasal syndrome (CBS)[13])– see Figure 1[14, 15]. Younger age at onset is associated with a higher likelihood of a non-amnestic presentation: 33% of cases with onset before age 65 have atypical presentations as opposed to just 6% of cases with onset after age 65 [16]. The high frequency of atypical presentations in young-onset AD has important clinical implications as it is associated with diagnostic delays and misdiagnosis. Appropriate use of biomarkers in the work up of patients with typical and atypical presentations can support timely, accurate AD diagnosis.

Furthermore, clinical phenotyping alone is insufficient to accurately identify underlying pathologies due to overlapping symptoms, signs, anatomical disease burden and co-pathologies[17, 18]. Indeed, up to 30% of pathologically confirmed cases of AD may be

misclassified when using clinical criteria alone[19]. There are many benefits of a definitive biological diagnosis: on an individual level it secures diagnostic accuracy[20], facilitates patient-centred care[1], informs symptomatic management[20, 21], and will be key in determining eligibility for novel disease modifying treatments (DMTs), while on a societal level there is emerging evidence to support possible reductions in rates of institutionalisation, mortality and health-care costs[22]. This needs to be balanced with careful attention to the potential harm of misdiagnoses[23]. Therefore, these tests should only be used in specific contexts by specialist clinicians.

The appropriateness of AD biomarker testing should be considered on a case-by-case basis at specialist clinics: important factors to consider include patients' age, preference, clinical phenotype and degree of cognitive and functional impairment[24] The decision to pursue AD biomarker testing should, ideally, be a shared decision-making process between the patient and the clinician. In the Irish setting, the current clinically available AD CSF biomarkers include: CSF Aβ42, Aβ40, phosphorylated-tau181(p-tau181) and total-tau(t-tau)). A typical AD CSF profile includes a low Aβ42 or Aβ42:Aβ40 ratio, indicating amyloid beta (Aβ) pathology; and high p-tau181, indicating AD tau pathology[20, 25] (Table 2). CSF t-tau, a marker of neurodegeneration, is frequently elevated but is not specific to an AD diagnosis, with very high levels (>1400 ng/ mL on INNOTEST assays) raising the possibility of Creutzfeldt-Jakob disease[20, 25].

Molecular imaging techniques can also provide useful diagnostic information in certain clinical situations: 18F-fluorodeoxyglucose positron emission tomography computerised tomography ([^{18}F]-FDG PET-CT) brain scan detects regional hypometabolism which is a non-specific marker of neurodegeneration[26], while amyloid positron emission tomography (PET) scans detect evidence of Aβ pathology *in-vivo*[2].

There is an urgent need to develop a standardised approach to the use of CSF and imaging biomarkers in the evaluation of cognitive impairment given the rapid evolution of diagnostic practices, increasing availability of biomarkers, and anticipated arrival of DMTs. It is expected that a confirmed biological diagnosis will be required before consideration for DMTs. For these reasons, we sought to develop recommendations on the appropriate use of AD biomarkers in the diagnostic evaluation of patients with cognitive impairment.

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Figure 1:

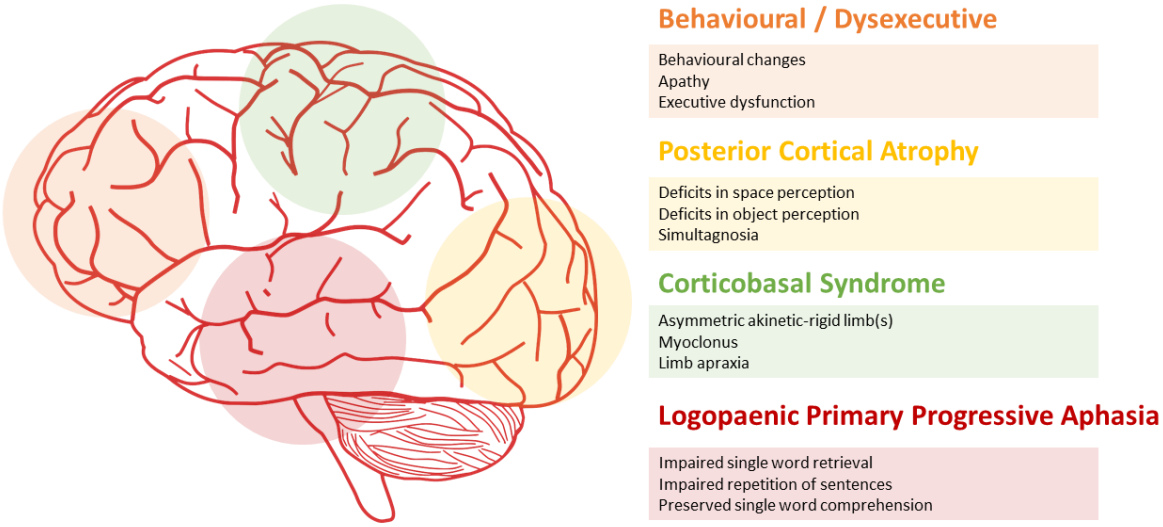

Figure 1 Legend: A simplified schematic of the clinical features and topography of non-amnestic AD phenotypes: behavioural/dysexecutive involving the frontal region (orange), posterior cortical atrophy involving the parieto-occipital region (yellow), corticobasal syndrome involving the fronto-parietal region (green), and logopenic primary progressive aphasia involving the dominant temporo-parietal region (red).

Methods:

In July 2024, the National Dementia Services unit of the Health Service Executive convened a working group focused on biological approaches to the diagnosis of AD and other dementias. This group comprised expert senior clinicians from each of the anchor specialties involved in dementia diagnosis (Neurology, Geriatric Medicine and Old Age Psychiatry), along with representation from General Practice, and the Alzheimer's Society of Ireland. The group was tasked with developing recommendations on the use of AD biomarkers in the evaluation of patients with cognitive impairment.

Recommendations:

When to consider pursuing a biological diagnosis of Alzheimer's disease?

This is a shared decision between the patient and the clinician. It takes into account patient preference, feasibility of testing and access to relevant resources. Pursuit of a

biological AD diagnosis should be considered in patients who (1) meet core clinical criteria for probable AD-mild cognitive impairment (AD-MCI) or mild AD-dementia; (2) persistent, progressing or unexplained MCI; (3) MCI or mild dementia with age onset <65 years, where AD is in the differential diagnosis; or (4) a non-amnestic AD phenotype e.g. lvPPA[14], behavioural/dysexecutive[12], PCA[11] or CBS[27] (Table 3). An important consideration when ordering and/or interpreting amyloid biomarkers is that the negative predictive value reduces with increasing age: the proportion of people with normal cognition and biomarker evidence of amyloid pathology is approximately 18% at 50 years, 25% at 60 years, 33% at 70 years and 43% at 80 years[28, 29]. It is anticipated that a biological diagnosis will be a prerequisite for future DMTs. These recommendations are limited to AD-specific CSF and imaging biomarkers, as further research is needed to determine the clinical application of AD-specific blood biomarkers. In particular, patients aged <50 years old with cognitive or behavioural symptoms need careful neurological assessment before embarking on an assessment of AD biomarkers. Similarly, these recommendations are not applicable to rapidly progressive cognitive impairment which involves a broader differential diagnosis including autoimmune and prion diseases[30]. These recommendations also do not address the use of complementary neurodegenerative biomarkers e.g. neurofilament-light [31] or α-synuclein[32,33]. It is increasingly recognised that neurodegenerative disorders often have co-existing molecular pathologies (e.g. α-synuclein, TDP-43, or vascular)[34, 35], but most molecular-specific biomarkers are not currently widely available[10].

What fluid and imaging biomarkers to use?

1. Cerebrospinal fluid biomarkers

In the Irish context, CSF biomarkers are the first-line recommended test when pursuing a biological AD diagnosis [10]. The core CSF biomarkers include: Aβ42 and Aβ40, indicating Aβ pathology; p-tau181, indicating AD tau pathology; and t-tau, which is a non-specific marker of neurodegeneration[2, 20]. The typical CSF profile in AD is low Aβ42, high p-tau181 and high t-tau[25, 29]. The different combination of AD biomarkers that are consistent with AD are highlighted in Table 2. CSF ratios (Aβ42:Aβ40, p-tau181:Aβ42; t-tau:Aβ42) have better concordance with amyloid-PET than individual CSF biomarkers[36-40]. In comparison to amyloid-PET, CSF biomarkers are more widely available, significantly cheaper[29], and have the potential to offer additional information about co-pathologies[2]. Lumbar punctures (LPs) are required to obtain CSF samples. It is well established that LPs are widely-accepted, safe and well-tolerated by patients in the evaluation of cognitive impairment[41, 42]. International guidelines have recommended a harmonised protocol for pre-analytical sample collection, handling and storage[43]. This involves collecting CSF samples via drip method directly into standardised low-binding polypropylene tubes[43]. The sample should be collected after the first 2mls, but before 20mls of the sample[43]. CSF should not pass through a manometer or be collected in or decanted from routine containers because this will result in artefactual

lowering of Aβ biomarkers[29, 43]. The exact tube and filling volume depends on individual laboratory recommendations[43]. CSF samples should reach the referring institution laboratory in a timely manner[29]. Initial processing involves centrifugation, distributing aliquots into polypropylene tubes, freezing and transporting to the testing site for analysis[25, 29,43]. Most international laboratories use automated immunoassay analysers measuring the core AD CSF biomarkers[25]. The most commonly used CSF ratio is Aβ42:Aβ40; but p-tau181:Aβ42 and t-tau:Aβ42 are also used[25]. 'Real-world' international laboratory experiences indicate that cut-off values are determined by a combination of manufacturer guidelines, other laboratories, internal data, or academic literature[25]. It is important to consider the contributions of patient-specific factors, pre-analytical handling and analytical processes when interpreting results[25]. There are currently two accredited operational laboratories testing CSF AD biomarkers in Ireland (Tallaght University Hospital and St. James's Hospital); ideally routine AD biomarker testing should be performed within nationally accredited laboratories in order to standardise sample analysis and result interpretation.

2. Imaging biomarkers:

Imaging biomarkers recognised in the diagnostic criteria of AD include MRI brain scan[2], [^{18}F]-FDG PET-CT brain[2], amyloid-PET and tau-PET brain[2, 10]. These can be sub-classified into AD-specific (amyloid-PET, tau-PET) and non-specific markers of neurodegeneration (volumetric MRI brain and [^{18}F]-FDG PET-CT brain). Access to AD-specific molecular imaging is not straightforward: Tau-PET is not currently available clinically in Ireland, while amyloid-PET is not widely available. Other imaging modalities used in the assessment of neurodegenerative disorders, ^{123}I-labeled 2β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl)nortropane [^{123}I]FP-CIT dopamine transporter imaging (DaTSCAN) and Iodine-123 metaiodobenzylguanidine (MIBG) cardiac scintigraphy are also briefly discussed.

a) MRI

MRI brain scan is the first-line recommended imaging modality in suspected cases of AD[44]. MRI brain scans are used to assess regional pattern of atrophy, burden of vascular disease and exclude structural causes of cognitive impairment e.g. brain tumour. The standard MRI brain sequences that should ideally be performed in the evaluation of patients with cognitive concerns include: 3D T1 volumetric acquisition with axial, coronal and sagittal reconstructions; axial T2-weighted; axial fluid attenuated inversion recovery (FLAIR); axial diffusion weighted imaging (DWI); and axial susceptibility weighted imaging (SWI)[45]. Neurodegenerative disorders have different patterns of regional atrophy depending on the clinical phenotype and underlying pathology[46]. In amnestic AD, there is often early hippocampal atrophy, followed by progressive involvement of the temporoparietal regions, and ultimately generalised cortical atrophy[44, 46]. Qualitative visual rating scores of medial temporal lobe atrophy (MTA) are calculated based on (1) the width of the choroid fissure, (2) width of the temporal horn of the lateral ventricle, and (3) height of the hippocampus using

coronal T1-weighted images of the hippocampus at the level of the anterior pons (Table 4; Figure 2)[46-48]. It is an ordinal scale ranging from 0-4, indicating progressive atrophy. MTA score interpretation is age-specific with proposed optimal cut-offs for ages <65, 65-74, 75-84 and ≥85 suggested as ≥1.0, ≥1.5, ≥ 2.0 and ≥2.0 respectively[49]. MTA is also described in other neurodegenerative disorders, but is more suggestive of AD, particularly if combined with parietal atrophy[50]. In certain cases, CT brain is a reasonable alternative structural imaging modality if MRI is contra-indicated/not possible. This should include reconstructions in axial, coronal and sagittal planes to assess for specific patterns of atrophy, ideally with thin slices of the hippocampi.

Figure 2:

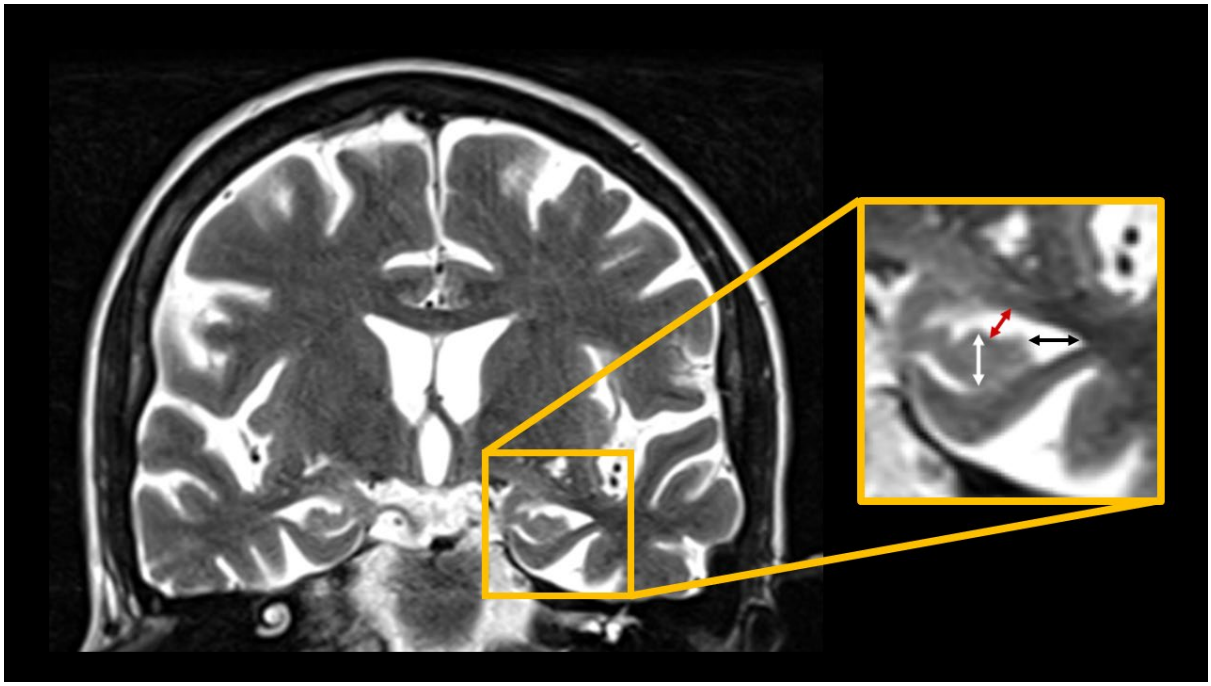

Figure 2: Coronal T2 sequence of MRI brain. Medial temporal lobe atrophy scale measures labelled: width of choroid fissure (red); height of hippocampus (white); and width of temporal horn (black)

b) [18 F]-FDG PET-CT brain

[18 F]-FDG PET-CT brain measures glucose metabolism, which is reduced in the setting of neuronal dysfunction, inferring non-specific neurodegeneration[26]. Statistical mapping is widely used for image interpretation and analysis, which enables standardised depiction of the location and severity of pathology. In typical AD, posterior cingulate cortex, precuneus, and temporal hypometabolism is described[26]. Similar to structural imaging, AD phenotype-specific patterns that mirror patterns of cognitive dysfunction and neurodegeneration are recognised[26]. In suspected neurodegeneration, [18 F]-FDG PET-CT brain should be reserved for select cases only after an MRI brain with volumetric sequence has been reviewed[51]. [18 F]-FDG PET-CT brain is most helpful in supporting diagnosis of suspected frontotemporal dementia or motor tauopathies (progressive supranuclear palsy (PSP), CBS)[51]. It may also be used in cases of diagnostic uncertainty[51].

c) Amyloid-PET

Amyloid-PET brain detects fibrillar Aβ plaques *in-vivo*[52]. The clinical interpretation of an amyloid-PET scan is classified as either 'positive' or 'negative'[52]. Amyloid-PET and CSF AD biomarkers exhibit high concordance and similar diagnostic accuracy in detecting Aβ pathology *in-vivo*[52]. However, amyloid-PET is more expensive than CSF[53]:with an estimated cost of €2000-2500 per scan versus €200 per CSF biomarker sample [52]. Furthmore CSF/PET discordant cases are most often CSF amyloid positive individuals, which if followed over-time, also become amyloid-PET positive[54]. The cost differential, apparent earlier change in CSF amyloid status, combined with the wider accessibility of CSF testing, means that amyloid-PET use should be restricted to carefully selected cases where CSF AD-biomarker testing is not appropriate or contraindicated. F

d) [123I]FP-CIT DaTSCAN and [123I]MIBG cardiac scintigraphy

It is often particularly challenging to clinically differentiate AD from dementia with Lewy bodies (DLB)[17]. In suspected cases of DLB, international consensus recommendations suggest beginning with [123I]FP-CIT DaTSCAN; and if this is normal, proceeding to [123I]MIBG cardiac scintigraphy[51]. [123I]FP-CIT DaTSCAN assesses presynaptic dopamine transporters in the striatum. An abnormal scan cannot differentiate DLB from idiopathic Parkinson's disease, multiple systems atrophy or PSP. [123I]MIBG cardiac scintigraphy assesses the postganglionic sympathetic cardiac nerves[55]. Diffuse denervation reliably discriminates DLB from other types of dementia[56]. Neither imaging modality is required if the core clinical criteria for 'probable' or 'possible' DLB are met[55]. This is with the caveat that sometimes AD and DLB pathologies co-exist and cannot be simplified into a binary classification[57, 58].

Discussion:

A biological diagnosis of AD should only be pursued in the appropriate clinical context (see Table 3) and should be a shared decision between the patient and the clinician. AD-

biomarker testing does not supplant the need for careful clinical phenotyping, routine laboratory testing and structural imaging. Within an Irish context, CSF AD biomarker (Aβ42, Aβ40, p-tau181, t-tau) testing should be first line when pursuing a biological AD diagnosis as it is cheaper, more widely accessible and, to a certain extent, scalable. [^{18}F]-FDG PET-CT or amyloid-PET are reserved for carefully selected cases. However, it is recognised that the pursuit of a biological diagnosis will bring considerable challenges in services often already struggling to deliver access to timely specialist assessments, diagnostic tests and post-diagnostic supports. Significant investment is needed in our workforce, laboratories, imaging and community care resources in order to deliver equitable, timely access to an accurate clinico-biological diagnosis for all appropriate patients[59]. It is anticipated that there will be additional costs and service demands with the administration of DMTs including the need for a skilled workforce, regular infusion therapies and serial surveillance MRI scans[60].

In addition to the clinically available biomarkers, there are emerging biomarkers that may be integrated into future diagnostic frameworks. Neurofilament light is a non-specific marker of neurodegeneration that is included in the diagnostic criteria for AD, but is not routinely tested[2]. It may have future applications in differentiating psychiatric diagnoses from neurodegenerative disorders[61]. The approval of α-synuclein seed amplification assays in CSF samples and skin biopsies is likely to transform diagnostic practices in the identification of α-synucleinopathies such as Parkinson's disease and DLB[32, 33]. Immunohistochemical detection of phosphorylated neuronal α-synuclein in skin biopsies is also promising[32]. Similarly, tau seed amplification assays in CSF samples and skin biopsies are being tested in 4R tauopathies (PSP and corticobasal degeneration), many of whom present with frontal-dysexecutive or other behavioural symptoms to memory clinics[62-64]. There has been rapid progress in the field of AD blood biomarkers, which could be transformative especially given the potential of certain measures e.g. p-tau217 to serve as an easily accessible, accurate, and cost-effective biomarker of AD pathology [65]. However further research is needed to establish diagnostic accuracy, optimal combinations of blood biomarkers, standardised pre-analytical test protocols, and assay validation before they are integrated into clinical practice[66]. It should be cautioned that AD blood biomarker testing should not be used at this time in primary care or obtained via self-testing commercial kits.

Our recommendations outline the appropriate use of AD biomarkers in the evaluation of cognitive impairment and suspected AD in the diagnostic assessments at Level 2 'Memory Assessment and Support Service (MASS)' or Level 3 ' Regional Specialist Memory Clinic' as per the 'Model of Care for Dementia in Ireland'. The role for AD biomarkers in Level 1 'Primary Care' is not defined, and requires further consultation. This is a rapidly evolving field, and as such, these recommendations will need timely revisions.

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Figure Legend:

Tables:

Table 1: Clinical Staging of Alzheimer's Disease (adapted from Jack Jr et al.[2])

Clinical Staging	Cognitive Impairment	Functional Impairment
'Transitional Decline' or 'Subjective Cognitive Decline'	Subjective	Independent
'Mild Cognitive Impairment' or 'Cognitive Impairment with Early Functional Impact'	Objective	Independent Minimal e.g. more time to complete ADLs
'Mild Dementia' or 'Dementia with Mild Functional Impairment'	Progressive Objective	Instrumental ADLs (shopping, food preparation, housekeeping, finances etc.)
'Moderate Dementia' or 'Dementia with Moderate Functional Impairment'	Progressive Objective	Basic ADLs (bathing, dressing, toileting, continence, feeding etc.)
'Severe Dementia' or 'Dementia with Severe Functional Impairment'	Progressive Objective	Fully dependent ADLs

Table 2: The interpretation of cerebrospinal fluid biomarker (adapted from Delaby et al[25])

Amyloid	p-Tau	t-Tau	Interpretation
↓	↑	↑	Consistent with AD
↓	↑	Normal	Consistent with AD
↓	Normal	↑	Atypical, but may be consistent with AD
↓	Normal	Normal	Consistent with Amyloidopathy*

*Amyloidopathy refers to biomarker evidence of Aβ deposition only. This is often one of the first CSF abnormalities detected in AD and can predate the onset of clinical symptoms; this CSF profile is not consistent with AD.

Table 3: When to consider pursuing a biological diagnosis of Alzheimer's disease

1.Meeting core clinical criteria for probable AD-MCI and mild AD-dementia
2. Persistent, progressing or unexplained MCI
3. MCI or mild dementia with onset age <65 years, where AD is in the differential diagnosis
4. Non-amnestic AD phenotype is being considered

Table 4: MRI medial temporal lobe atrophy scale (adapted from Mortimer et al.[46])

Scale	Width of choroid fissure	Width of temporal horn	Height of hippocampus
0	Normal	Normal	Normal
1	Mild increased	Normal	Normal
2	Moderate increased	Mild increased	Mild reduced
3	Marked increased	Moderate increased	Moderate reduced
4	Marked increased	Marked increased	Marked reduced

Declarations of Conflicts of Interest

None declared.

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