European intersocietal recommendations for the biomarker-based diagnosis of neurocognitive disorders

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Lancet Neurol 2024; 23: 302–12

See Comment page 225

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The recent commercialisation of the first disease-modifying drugs for Alzheimer's disease emphasises the need for consensus recommendations on the rational use of biomarkers to diagnose people with suspected neurocognitive disorders in memory clinics. Most available recommendations and guidelines are either disease-centred or biomarker-centred. A European multidisciplinary taskforce consisting of 22 experts from 11 European scientific societies set out to define the first patient-centred diagnostic workflow that aims to prioritise testing for available biomarkers in individuals attending memory clinics. After an extensive literature review, we used a Delphi consensus procedure to identify 11 clinical syndromes, based on clinical history and examination, neuropsychology, blood tests, structural imaging, and, in some cases, EEG. We recommend first-line and, if needed, second-line testing for biomarkers according to the patient's clinical profile and the results of previous biomarker findings. This diagnostic workflow will promote consistency in the diagnosis of neurocognitive disorders across European countries.

Introduction

International societies and associations advocate for the early, timely, and accurate diagnosis of Alzheimer's disease and related conditions,[1–3] and indeed biomarkers are available that will help to achieve this goal.[4] The advent of expensive disease modifiers for Alzheimer's disease will require increasingly accurate diagnosis so that they can be targeted to those who will benefit the most.[5,6]

A diagnosis of Alzheimer's disease can be ascertained through either lumbar puncture and measurement of CSF biomarkers (ie, phosphorylated tau [p-tau] or total tau [t-tau], amyloid Aβ42, and Aβ42-to-Aβ40 ratio [Aβ42/40]), or amyloid-PET. However, these biomarkers are not always the most informative in individuals attending memory clinics. 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG) PET gives information on patterns of cortical hypometabolism that are indicative of neurodegenerative diseases (eg, Alzheimer's disease, frontotemporal dementia, Lewy body disease, motor tauopathies). Brain SPECT with [^{123}I] N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl) nortropane ([^{123}I]FP-CIT) reveals impairment of the nigrostriatal pathway, and cardiac [^{123}I]-meta-iodobenzyl-guanidine ([^{123}I]MIBG) scintigraphy reveals impairment of the postganglionic sympathetic heart terminals, both of which characterise Lewy body disease. Additionally, EEG can show electrical abnormalities of the cortex in prion diseases, encephalopathies from several causes, Lewy body disease, and late-onset epilepsy. Polysomnography can detect the rapid eye movement (REM) sleep behaviour disorder that is common in Lewy body disease and other neurodegenerative conditions. Tau-PET with [^{18}F] flortaucipir can consistently detect and quantify tauopathy of Alzheimer's disease.[4]

Guidelines and recommendations have been developed to help clinicians use diagnostic biomarkers rationally and effectively.[7–22] However, these guidelines are only partly helpful in everyday clinical practice, as most of them are either biomarker-centred[7,8,15–17] or disease-centred,[9–14,22] and do not account for multiple diagnostic options and the availability of multiple biomarkers for sequential or parallel use.[18] Those guidelines that do account for these factors either reflect only national expertise,[19] or have been developed by non-representative groups of experts.[15] As a result, the choice of biomarker is often influenced more by organisational and logistical factors than by clinical and patient-related factors.[19,20]

With an aim to overcome these described limitations, delegates from 11 European scientific societies and organisations, and a patient advocacy association (Alzheimer Europe), have united efforts to define a patient-centred biomarker-based diagnostic workflow to be used in memory clinics. Delegates used their own expertise and a review of recent literature to reach consensus on numerous specific questions defined by an independent steering committee. A Delphi voting procedure was followed, from November 2020 to June 2022, to reach consensus.[23] The methodology and theoretical foundations of this exercise have been detailed in a previous paper.[24] In the present Personal View, we report the diagnostic workflow. We also describe the six Delphi rounds that generated the workflow in the appendix (pp 2–11). Biomarkers of interest included traditional CSF biomarkers (Aβ42, Aβ42/40, p-tau, and t-tau), [^{18}F]FDG PET, amyloid-PET, [^{123}I]FP-CIT SPECT, cardiac [^{123}I]MIBG scintigraphy, tau-PET with flortaucipir (the only commercially available tau tracer), polysomnography, and resting-state EEG according to the principal diagnostic criteria for neurocognitive diseases and guidelines.[24]

Diagnostic workflow

The overall structure and guiding principles of the diagnostic workflow were defined in a preliminary first

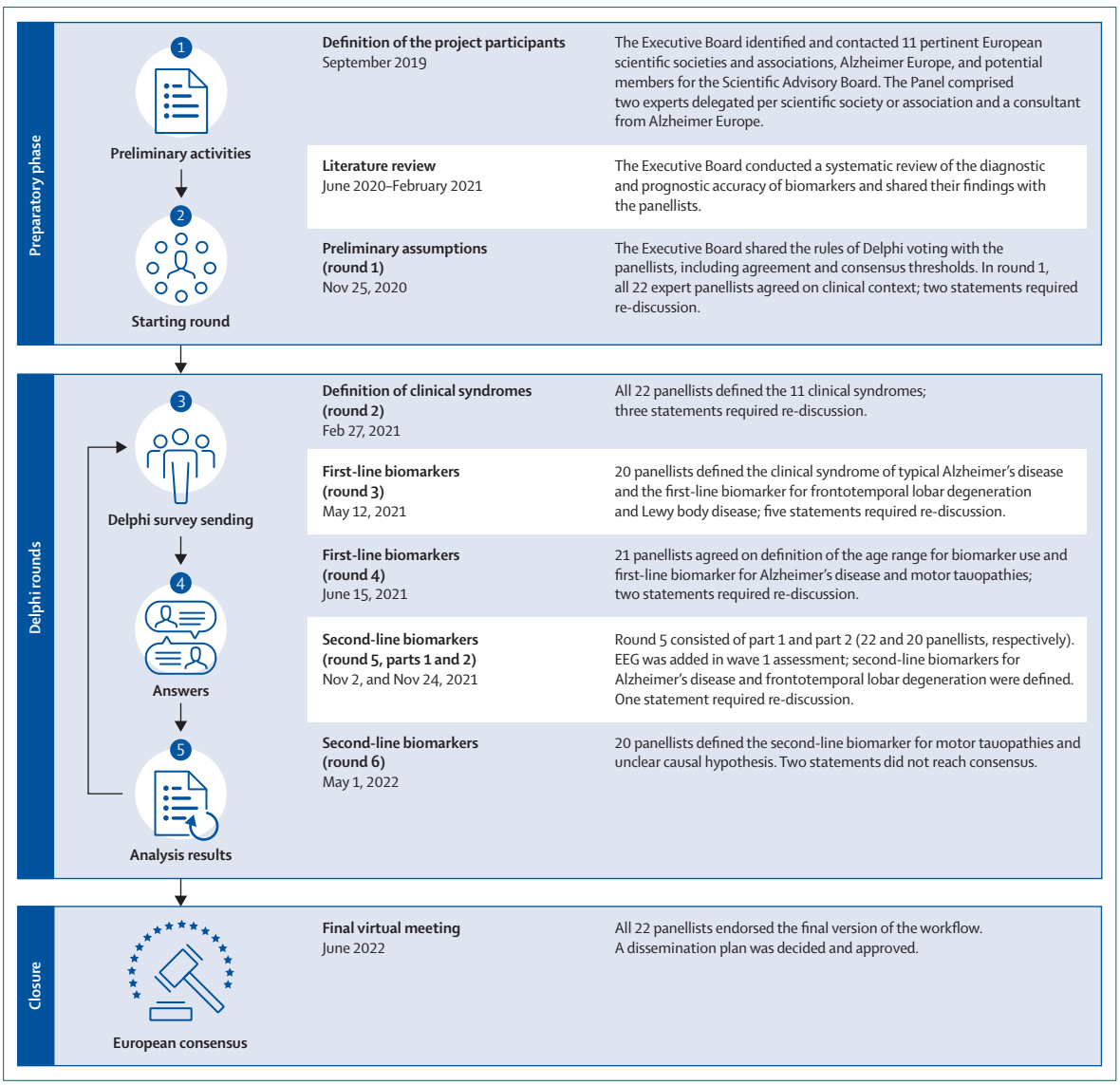

Figure 1: **Study design and chronogram**
The activities in charge of the Executive Board and Delphi panel are concisely summarised. A more detailed description of the preparatory phase can be found in the 2022 publication by Festari and colleagues.[24] The decision tree of the Delphi rounds is graphically illustrated in the appendix (p 7), and the composition of the Executive Board and Delphi panel is also provided (appendix p 6).

Delphi round described in full in a previous publication.[24] The methods of this first Delphi round are also summarised in figure 1. We also report the statements discussed during the Delphi procedure, detailing the proportion of panellists who were in agreement (appendix pp 8–9). Strong agreement was defined as over 70% agreement among panellists, and moderate agreement as 50–69% agreement among panellists. Briefly, more than 80% of panellists agreed that: specific diagnostic frameworks, reimbursement, and logistical factors should not be considered in the development of the workflow; the workflow should be person-centred (ie, developed around an individual's clinical features); clinical syndromes should serve as the entry point for biomarker selection; diagnostic thinking should consist of assessing signs and symptoms, excluding those signs and symptoms that are caused by a non-neurodegenerative condition; and the workflow should determine the molecular cause of neurodegeneration.

The workflow was developed on the basis of common practices in memory clinics.[25,26] These practices comprise four waves, starting from a clinical examination and assessment of the person's complaints, excluding secondary causes for the cognitive complaint, and staging patients as having mild cognitive impairment (MCI) or mild dementia (wave 0). Patients are then categorised into clinical syndromes (wave 1), summarising the

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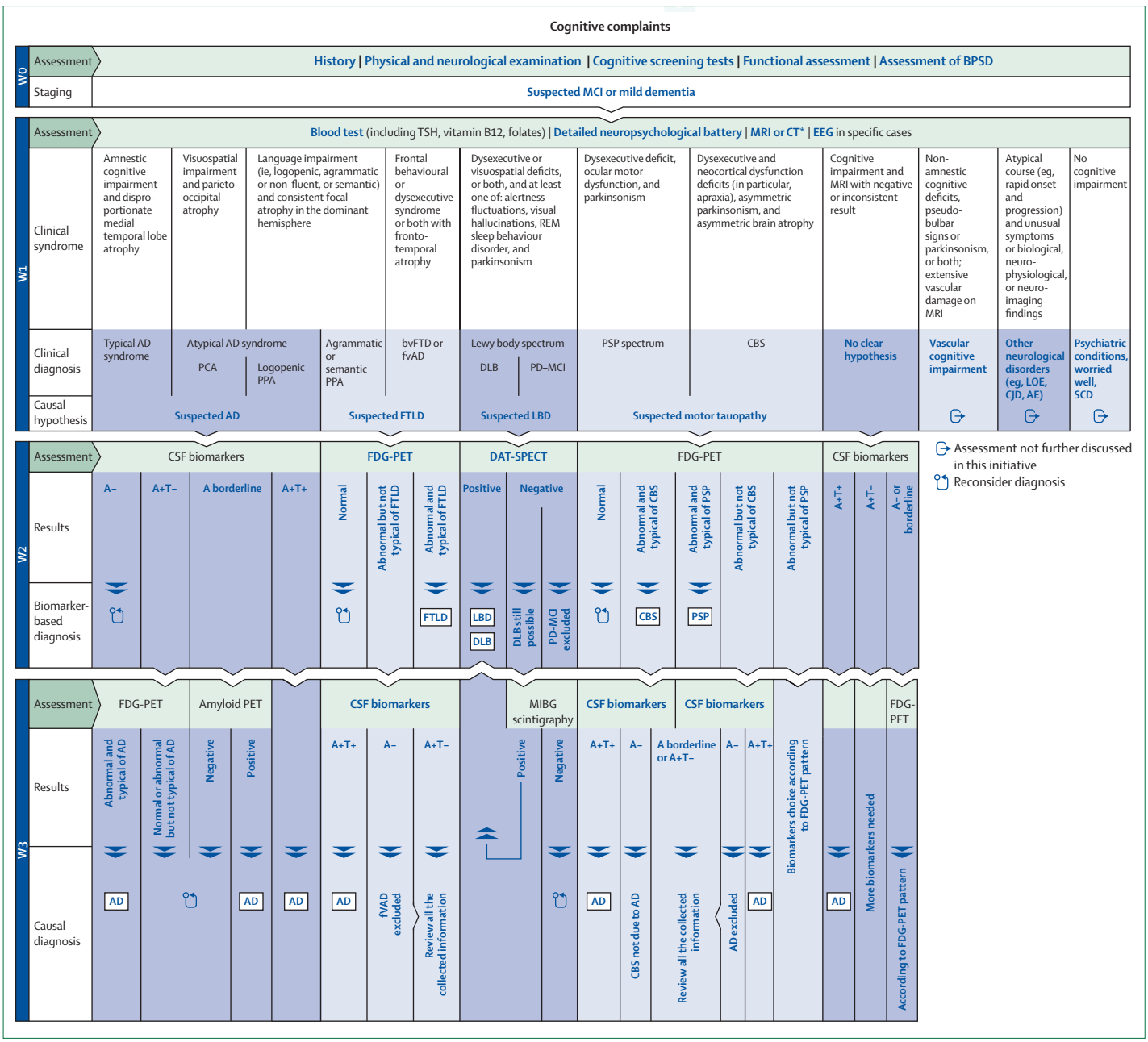

Figure 2: **The consensus diagnostic workflow**
The workflow unfolds in four waves. A basic assessment in wave 0 (W0) is followed by wave 1 (W1) allowing categorisation of individuals by their clinical syndromes and for a causal hypothesis to be issued. First-line biomarker assessment might follow in wave 2 (W2) and, if indicated, second-line biomarker assessment in wave 3 (W3). Biomarkers indicated in bold blue font denote strong agreement among panellists (≥70%), whereas those in black font denote moderate agreement (50–69%). Biomarker use: strongly recommended for individuals younger than 70 years; recommended depending on individual clinical characteristics in those aged 70–85 years; and not recommended for individuals older than 85 years. A– and A+ denote biomarker negative and positive, respectively, for brain amyloidosis, and T– and T+ denote biomarker negative and positive, respectively, for tauopathy. AD=Alzheimer's disease. AE=autoimmune encephalitis. BPSD=behavioural and psychological symptoms of dementia. bvFTD=behavioural variant of frontotemporal dementia. CBS=corticobasal syndrome. CJD=Creutzfeldt–Jakob disease. DAT=dopamine transporter. DLB=dementia with Lewy bodies. FDG=[^{18}F]fluorodeoxyglucose. FTLD=frontotemporal lobar degeneration. fvAD=frontal variant of Alzheimer's disease. LBD=Lewy body disease. LOE=late-onset epilepsy. MCI=mild cognitive impairment. MIBG=meta-iodobenzylguanidine. PCA=posterior cortical atrophy. PD=Parkinson's disease. PPA=primary progressive aphasia. PSP=progressive supranuclear palsy. REM=rapid eye movement. SCD=subjective cognitive decline. TSH=thyroid-stimulating hormone. *CT should be performed only if MRI is unavailable or contraindicated.

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patient's salient clinical and cognitive characteristics and structural neuroimaging findings. Clinical syndromes lead to hypotheses of disease causation that direct the selection of first-line biomarkers in wave 2. Second-line biomarkers might follow in wave 3, according to the results of first-line biomarkers.

The final diagnoses were considered causal when biomarkers allow the molecular pathology to be ascertained

(as is the case for amyloidosis and tauopathy in Alzheimer's disease), and biomarker-based in all other cases (figure 2). Figure 2 shows the diagnostic workflow, arranged into consecutive waves from wave 0 to wave 3. The development of the workflow is described in the following sections. The biomarker guidelines and diagnostic criteria, used as references by panellists in the creation of the diagnostic workflow, are specified in the text and detailed elsewhere.[24]

Wave 0—staging

The panel endorsed the guidelines for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia that were developed by the European Federation of Neurological Societies (EFNS), and its revisions.[25–27] Accordingly, the first visit by an individual to a specialised outpatient service should include the collection of family, medical, social, and cognitive history, neurological and physical examinations, cognitive screening tests, and assessment of daily function and behavioural and psychological symptoms. Whenever possible, an informant (eg, a family member, primary-care physician, caregiver) should complement the patient's perspective. By integrating these data, the clinician can exclude some secondary causes of cognitive complaints (psychiatric, somatic, iatrogenic, and neurological) and issue a temporary staging hypothesis of MCI or mild dementia. People with suspected MCI or mild dementia and no alternative explanation for the cognitive complaint should proceed to further diagnostic investigations in wave 1. Patients with moderate-to-severe dementia should not typically undergo this exercise because they are generally not considered appropriate for a biomarker-based diagnosis.[7,8,15,16,18,21]

Wave 1—clinical syndromes

The panel endorsed first-line investigations indicated by the EFNS guidelines.[25–27] These investigations consist of: routine blood tests in all cases and other physical tests in specific cases (urinary tests, chest x-ray, etc), to exclude systemic diseases that might be causing the cognitive impairment, and to identify comorbidities or potentially treatable causes of cognitive impairment; a thorough neuropsychological evaluation of the main cognitive domains; and structural neuroimaging with MRI with dedicated sequences,[28] or CT when MRI is not feasible or contraindicated. Structural neuroimaging allows exclusion of treatable causes of dementia (eg, meningioma, normal pressure hydrocephalus), quantification of vascular changes, and identification of suggestive cortical atrophy patterns (eg, medial temporal atrophy, disproportionate or asymmetrical frontal and temporal atrophy, occipital atrophy, pontine atrophy).

Panellists unanimously endorsed resting state EEG with expert visual reading in specific circumstances, such as history of seizures, alterations of consciousness, possibly due to epilepsy or encephalopathy, and atypical subacute course.[29] Patterns of lateralised or bilateral epileptiform discharges or abnormalities, or slow (sometimes triphasic and periodic) waves support a diagnosis of late-onset epilepsy, prion disease, or toxic, metabolic, septic, autoimmune, and anoxic encephalopathies.[30–32] The panel strongly agreed to discourage the systematic use of EEG in patients with MCI or mild dementia and discourage looking for positive diagnostic information on specific types of degenerative cognitive disorders, except in cases of suspected dementia with Lewy bodies with REM sleep behaviour disorder.[33]

The panel strongly endorsed (agreement >70%) assigning patients to the distinctive clinical syndromes resulting from the evaluations just described (appendix pp 7–9), consisting of: typical Alzheimer's disease with a prominent amnestic profile,[9,22] or atypical Alzheimer's disease syndromes presenting as posterior cortical atrophy,[34] logopenic variant of primary progressive aphasia,[11] and frontal or behavioural variants,[10] in which Alzheimer's disease is generally the underlying pathophysiology; primary progressive aphasia manifesting as non-fluent, agrammatic or semantic disorders,[11] and behavioural variants of frontotemporal dementia,[10] which are predominantly manifestations of frontotemporal lobar degeneration; prodromal or overt dementia with Lewy bodies[12,33] and Parkinson's disease with MCI,[35] which are both expressions of the Lewy body disease spectrum; the spectrum of progressive supranuclear palsy[13] and corticobasal syndrome,[14] which are considered motor tauopathies because they present with an atypical parkinsonism and have four-repeat (4R) tau proteinopathy as the most frequent substrate; and vascular cognitive impairment.[36–38] Other neurodegenerative diseases, such as amyotrophic lateral sclerosis and multiple system atrophy, have not been included in the workflow because cognitive symptoms usually appear after motor symptoms, and diagnosis is usually made in settings other than memory clinics.

When the wave 0 and wave 1 assessments are indicative of cognitive impairment, but neuropsychological and structural imaging findings are discordant (eg, dysexecutive or attentional deficits with prominent cortical atrophy in posterior regions) and a reasonably well founded diagnostic hypothesis cannot be put forward, the panel endorsed looking for further evidence to rule in or rule out a diagnosis of a neurocognitive disorder. The panel strongly agreed to subsume rare neurological disorders, such as autoimmune encephalitis, prion diseases, late-onset epilepsy, and paraneoplastic syndromes, under the "other neurological disorders" category, because all these diseases present an atypical course of cognitive impairment (eg, subacute onset and rapid progression) and other unusual symptoms (cerebellar signs, chorea, myoclonus, generalised hyperexcitability, etc); distinctive biological, neurophysiological, and neuroimaging findings for these diseases should be actively researched.

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See **Online** for appendix

In the final virtual meeting, the panel unanimously endorsed the proposal by the Executive Board not to move forward with causal biomarkers when a complete neuropsychological examination is normal, possibly indicative of a subjective cognitive disorder or a psychiatric condition, and for the so-called worried well (ie, individuals who are concerned due to, for example, a family history of dementia, as stipulated by code Z71.1 in the International Classification of Diseases, tenth revision).

First-line (wave 2) and second-line (wave 3) biomarkers

The following five workflow branches (ie, branch for Alzheimer's disease, frontotemporal lobar degeneration, Lewy body disease, motor tauopathy, and no clear hypothesis) strive to reach a causal diagnosis whenever possible, by testing a single first-line biomarker (wave 2). A second-line biomarker is proposed if the former yields an inconclusive or equivocal result (wave 3). The panel reached moderate agreement (68%) on recommending diagnostic biomarkers routinely in patients younger than 70 years and only in exceptional cases in patients older than 85 years (57%). By inference, in patients aged 70–85 years, the use of diagnostic biomarkers might be driven by individual clinical features (eg, functional status, comorbidities, patient preferences).

The Alzheimer's disease branch

The panel agreed on using CSF biomarkers in wave 2 in people with suspected Alzheimer's disease (75% in agreement after re-discussion). The panel unanimously agreed that the diagnostic process is conclusive for an Alzheimer's disease cause when CSF biomarkers indicate brain amyloidosis (based on reduction of CSF Aβ42 or Aβ42/40 ratio) and tau pathology (based on elevated p-tau protein).[39] When amyloid readings are unequivocally negative, Alzheimer's disease is excluded, and the diagnostic suspicion requires reconsideration (65% of panellists in agreement). Age-associated pathologies other than Alzheimer's disease, such as primary age-related tauopathy and TDP-43 pathology, are diagnostic options, but specific in-vivo biomarkers are absent.

The panel discussion also covered some peculiar scenarios of CSF biomarker results, all needing a second-line diagnostic biomarker to ascertain Alzheimer's disease cause. The expert panel was in moderate agreement (with a range of agreement of 50–56%) in favour of amyloid-PET when CSF amyloid readings are borderline, but the diagnosis of Alzheimer's disease is still the most probable. If amyloid-PET is positive, a final causal diagnosis of Alzheimer's disease can be made; otherwise, the diagnostic hypothesis needs to be critically reviewed. In the event that CSF biomarkers are unequivocal for isolated amyloidosis without concurrent tau pathology (ie, A+T–), a moderate agreement (58–64%) supported use of [^{18}F]FDG-PET to ascertain the topography of hypometabolism as a proxy for neuronal damage distribution. A typical hypometabolic pattern, mainly involving the posterior cingulate cortex, precuneus, posterior temporoparietal cortex, and medial temporal lobe in various combinations, will support the diagnosis of Alzheimer's disease;[40] alternatively, in the case of an atypical pattern for Alzheimer's disease, the previous findings will need to be critically reconsidered.

The frontotemporal lobar degeneration branch

The panel strongly agreed (76%) on use of [^{18}F]FDG-PET in wave 2 when the causal hypothesis is frontotemporal lobar degeneration. A typical and distinctive pattern of hypometabolism is required to confirm the diagnosis of frontotemporal lobar degeneration and to conclude the diagnostic workup (79%). The behavioural variants of frontotemporal dementia frequently occur with hypometabolism of the frontal or anterior temporal regions; non-fluent primary progressive aphasia is characterised by hypometabolism of the left posterior fronto-insular cortex; and semantic primary progressive aphasia is characterised by hypometabolism of the anterior temporal regions. Conversely, a normal scan makes a neurodegenerative disorder highly improbable. The panel strongly agreed (89%) on a second-line biomarker when [^{18}F]FDG-PET displays an atypical hypometabolic pattern that is not typical for frontotemporal lobar degeneration (eg, also involving the posterior regions). CSF biomarkers are preferred with moderate agreement (69%). A profile of CSF A+T+ (ie, presence of amyloidosis and tau pathology) will be in favour of Alzheimer's disease manifesting with frontal behavioural, dysexecutive, or logopenic symptoms.[9,41] In the event that CSF biomarker findings are unequivocal for isolated amyloidosis without tauopathy (ie, A+T–), it is probable that amyloidosis is an incidental finding or a co-pathology to another molecular cause primarily driving cognitive symptoms (eg, TDP-43). The clinician in this case should critically reconsider the previous findings and decide whether to proceed with a diagnosis or choose a potential third-line biomarker. This recommendation was proposed by the Executive Board and unanimously endorsed by the panel in the final virtual meeting. Third-line biomarkers were not discussed in this exercise.

The Lewy body disease branch

The panel strongly recommended (71%) use of nigrostriatal degeneration imaging with [^{123}I]FP-CIT (DAT-SPECT) in wave 2 when the causal hypothesis is Lewy body disease. In the case of a negative DAT-SPECT and when the clinical picture is still compatible with dementia with Lewy bodies, a moderate agreement (55% after re-discussion) was reached in favour of cardiac [^{123}I]MIBG scintigraphy as a wave 3 biomarker to identify specific denervation of postganglionic sympathetic heart terminals. This decision was made in view of prodromal dementia with Lewy bodies featuring Lewy body pathology in the limbic and neocortical regions with sparing of the substantial nigra.[12,42]

The motor tauopathy branch

When the causal hypothesis is a motor tauopathy, [18F]FDG-PET was recommended with moderate agreement (65%, after re-discussion) as the first-line diagnostic biomarker. The rationale for the choice was the negative predictive value for neurodegeneration in the case of a normal scan and the use of hypometabolic patterns to provide positive information for the differential diagnosis.[43–46]

A typical pattern of hypometabolism in the medial frontal gyrus, anterior cingulate cortex, pons, and ventral striatum[14] will indicate progressive supranuclear palsy (67% in agreement). The panel nearly unanimously agreed (88%) that a second-line diagnostic biomarker should be used when [18F]FDG-PET shows an atypical hypometabolic pattern, which is not typical for progressive supranuclear palsy but does not preclude a diagnosis for this disease. In the initial voting session, the panel reached a moderate agreement (57%) on the application of PET with tau tracers. The Executive Board noticed a potential misinterpretation after carefully reading the panellists' argumentations because many mentioned second-generation tau tracers. However, these tracers are not yet approved for clinical use in Europe and the USA, and validation is still ongoing.[47,48] The issue was brought back for discussion with the necessary clarifications on the type of tau tracer to be considered, namely [18F]flortaucipir. Indeed, this tracer binds predominantly to Alzheimer's disease-typical 3R-4R tau isoforms and has wider availability and stronger evidence of clinical validity than other tau tracers.[49] The panel was unable to come to a consensus on which second-line biomarker should be prioritised and concluded that the hypometabolism pattern and associated clinical picture should guide the clinician on an individual patient basis.

The finding of a typical pattern of asymmetric hypometabolism of the parietal and frontal cortex, thalamus, and basal ganglia[16] is consistent with corticobasal syndrome, but should prompt further investigation to ascertain its cause (87% in agreement after re-discussion). The panel strongly recommended (71%) CSF biomarkers to rule out an underlying Alzheimer's disease pathophysiology, because this disease is the most common alternative to motor tauopathy.[50,51] Otherwise, negative CSF amyloid markers are consistent with tau-related corticobasal degeneration.[14] When [18F]FDG-PET shows an abnormal hypometabolic pattern atypical for corticobasal syndrome, but such a diagnosis is still plausible, the panel almost unanimously agreed (88%) to recommend CSF biomarkers as second-line diagnostic biomarkers. These biomarkers should either support (A+T+) or exclude (A–) an Alzheimer's disease cause (86% in agreement after re-discussion). When CSF biomarkers are inconclusive, as is the case for borderline or isolated amyloidosis (ie, A+T–), the panel advised that the previous findings should be critically reconsidered, leaving the clinician to decide whether to make a diagnosis or request more investigations.

The no clear hypothesis branch

The panel was in moderate consensus (55% after re-discussion) on use of CSF biomarkers as first-line biomarkers in cases of no clear-cut clinical diagnostic hypothesis, as Alzheimer's disease is the most frequent cause of neurodegenerative disease in these cases. When CSF biomarkers are inconclusive or negative for Alzheimer's disease, the panel strongly advised (78%) a second biomarker, and proposed [18F]FDG-PET with moderate agreement (54%). Hypometabolic patterns will allow the clinician to reinitiate their diagnostic reasoning.

The panel was cautious when interpreting isolated amyloidosis on CSF analysis (ie, A+T–) in scenarios in which the clinical profile is not suggestive of Alzheimer's disease, as this finding might be incidental. Albeit moderately concurring (65%) on the need for a second-line biomarker, the panellists disagreed over which biomarker to prioritise. The heterogeneity of opinions, the degree of granularity, and the unique characteristics of this branch of the workflow prompted the decision to halt the Delphi process at this stage. The advice from the panel is to critically reconsider the previous findings and leave the choice to the clinician on a case-by-case basis. This recommendation was initially proposed by the Executive Board and was subsequently unanimously endorsed in the final virtual meeting.

Conclusions and future directions

The commercialisation of monoclonal antibodies targeting amyloid pathology of Alzheimer's disease makes the need for an accurate and rational causal diagnosis of patients attending memory clinics an even more pressing issue than in the recent past. In an ideal context with unlimited resources, symptoms in individuals attending a memory clinic might be investigated with a large panel of biomarkers to achieve the most accurate possible diagnosis. In the real world, clinicians struggle with clinical, organisational, and budgetary constraints that restrict biomarker access and use; clinicians therefore aim to extract the largest possible amount of information from the lowest number of examinations. The workflow that we developed will help clinicians to choose the biomarker with the highest information yield in the clinical case scenarios most frequently encountered in the clinic.

The context for use of this workflow is specialist outpatient services for individuals with cognitive complaints. The workflow is not designed to be used at the general practice level, where the paucity of resources, time, and expertise hamper a thorough assessment of the patient's cognitive profile—the mandatory gateway to biomarker assessment. This workflow is not supposed to override disease-specific[9–14,22] and biomarker-specific guidelines, but to complement them.[7,8,15–17] This workflow is also not

devoted to the autosomal dominant forms of dementia, for which a suggestive family history and young age of onset require genetic counselling and assessment of gene mutations. To make the workflow applicable to different health-care systems, the Delphi panel did not assume any specific constraints, except biomarker approval for clinical use at the time of the Delphi exercise (2020–22). Health-care providers might wish to use the workflow to optimise resource use and harmonise patient care, and payers might wish to use it as a guide to optimise and harmonise biomarker reimbursement. National scientific societies might wish to translate the workflow into the different European regulatory and reimbursement environments,[52] promoting homogeneity of patient management across national regions and European countries.

The workflow was based on the reductionistic assumption of one diagnosis-one pathology, although it is well known that comorbid pathologies (amyloid β, tau, TDP-43, α-synuclein, vascular, and others) are very common, and even more so in older people (ie, individuals older than 70 years).[53] Pathological and in-vivo studies suggest that amyloid pathology modifies the clinical expression of at least dementia with Lewy bodies.[54,55] However, assigning a clinical weight to comorbid pathologies in individual patients attending memory clinics is beyond current possibilities. At present, biomarkers are only available in the clinic for Alzheimer's disease pathology (β-amyloidosis or 3R-4R tau pathology) and a causal diagnosis can be made for Alzheimer's disease only. The diagnosis of non-Alzheimer's disease pathologies (α-synuclein, TDP-43, and 4R tau) is indirectly inferred from biomarkers of downstream processes, such as nigrostriatal degeneration DAT-SPECT, cardiac sympathetic denervation ([^{123}I]MIBG scintigraphy), and brain glucose hypometabolism ([^{18}F]FDG-PET). Molecular biomarkers for non-Alzheimer's disease pathology are under active development but require more evidence to be implemented in the diagnostic process.[56–58] In this regard, the low agreement achieved on some Delphi rounds points to the questions that urgently need more scientific investigation.

Of all biomarkers addressed by the present exercise, resting state EEG was the most debated. The panel acknowledged the extensive literature showing group differences in resting state EEG markers for most neurodegenerative conditions.[59] However, resting state EEG was endorsed in a relatively restricted number of diagnostic questions, due to the general absence of clinically valid measures allowing discrimination of individual cases, and due to the paucity of superiority data comparing resting state EEG with other biomarkers (eg, visual assessment of resting state EEG *vs* DAT-SPECT in suspected Lewy body disease).

The clinical validity and usefulness of traditional biomarkers, including amyloid PET, are fairly well established and have not changed appreciably over the 20 months of the survey. On the contrary, evidence for novel biomarkers is relatively less abundant than for traditional biomarkers, but is rapidly accumulating. Ultra-sensitive immunoassays for Alzheimer's disease pathology, α-synuclein, neuroinflammation, neuro-degeneration, and synaptic damage in the blood and CSF have been qualified for research use and are being validated for use in the clinic.[60–64] However, as these immunoassays are currently not available for clinical use, they were not taken into account in the present Delphi exercise. When clinically validated, these immunoassays might revolutionise diagnostic practices and the diagnostic investigation of patients with cognitive complaints; accordingly, this workflow will then need to be deeply revised. More innovations might need to be included in a revised version of the workflow if further evidence is accrued on the clinical utility of first-generation and second-generation tau PET tracers. Evidence indicates that some CSF p-tau isoforms (eg, p-tau181 and p-tau217) might be more strictly associated with CSF and PET amyloid than tau markers, whereas CSF microtubule binding region-tau243 could be more specific for tau pathology.[65] CSF and plasma progranulin, a prognostic and predictive marker in oncology, might be used to screen patients with possible familial frontotemporal lobar degeneration.[66,67] In dual-phase amyloid-PET, an early scan (about 5 min after tracer injection) indexes cortical perfusion and seems an accurate proxy of cortical metabolism on [^{18}F]FDG-PET.[68] Magnetic resonance-based arterial spin labelling also provides cortical perfusion information and is a non-invasive and cost-effective

For the **Mendeley repository containing details of the literature search** see https://data.mendeley.com/datasets/8sxf8tvwgm/1

Search strategy and selection criteria

We adapted the literature review on biomarker accuracy performed for our previous Policy View published in 2017, and expanded it with a systematic review of published manuscripts available in the PubMed (MEDLINE) database from Jan 1, 2017, to Feb 28, 2021. We drafted search strings that required the following keywords and conditions: (1) population of interest: "MCI", "mild cognitive impairment", "DLB", "dementia with Lewy bodies", "FTD", "frontotemporal dementia", etc; (2) biomarkers: "amyloid" and "tau" (separately for CSF and PET), "FDG-PET", "DaT SPECT", "MIBG", "EEG", and "polysomnography"; (3) period of publication: from Jan 1, 2017, to Feb 28, 2021; and (4) publication type: only original research articles published in the English language, and no reviews. We retrieved 2200 articles in total. Each article was evaluated by coauthors (CF, MCR, FM, SO) to select those assessing accuracy, sensitivity, specificity, or area under the receiver operating characteristic curve to predict clinical progression to dementia or pathology in at least 50 patients with mild cognitive impairment with a follow-up of at least 3 years. Studies fulfilling the above criteria were absent for the less common disorders (ie, dementia with Lewy bodies, frontotemporal dementia, and primary progressive aphasia) and the less frequently studied techniques (ie, tau PET, dopamine transporter SPECT, and meta-iodobenzylguanidine scintigraphy). In these cases, we allowed cross-sectional studies, group size as low as 20, cognitive stage as low as mild dementia, and clinical or biomarker diagnosis as reference standard. Search strings and the full reference list are available as supporting information in a previous publication by Festari and colleagues published in 2022, and in the Mendeley online repository. Selected papers outside the calendar bounds of the literature search were included on the basis of their relevance of the topic.

candidate biomarker.[69,70] Resting state functional MRI, which assesses functional neural network connectivity, might be sensitive to the earliest neural dysfunction and compensatory events of neurodegenerative conditions.[71] Second-generation tau PET tracers, which are known valid markers of Alzheimer's disease,[47] seem sensitive to 4R motor tauopathies, such as progressive supranuclear palsy and corticobasal degeneration.[48] Limbic-predominant age-associated TDP-43 encephalopathy (also known as LATE) might find a place in the workflow once more biomarker data become available.[72] Transcranial magnetic stimulation seems sensitive to disease-specific abnormalities of cortical excitability in Alzheimer's disease, Parkinson's disease, frontotemporal lobar degeneration, and Lewy body disease.[73]

Notably, the availability of disease-modifying treatments should not be the only reason in support of an accurate biomarker-based diagnosis. Early detection allows access to treatments of proven efficacy, both pharmacological and non-pharmacological, guarantees proper handling of behavioural and psychiatric symptoms, allows access to clinical trials, and prevents iatrogenesis, such as the use of inadequate drugs or treatments with unproven efficacy for a specific diagnosis. Moreover, regardless of age and available treatment, the patient has the right to know the reason for their cognitive impairment with the precision allowed by current technology. The so-called value of knowing encompasses decisions on life arrangements, with relevant socioeconomic consequences. We also wish to stress that the panel endorses the value of knowing only for individuals who have diagnosed cognitive impairment, as measured with state-of-the-art neuropsychological tools. Biomarker assessment should not be offered in memory clinics to people with subjective cognitive decline in the absence of atypical cognitive test outcomes or individuals who are merely concerned about the preservation of their cognitive abilities (the so-called worried well). Care in these instances will be the domain of brain health services for the prevention of dementia, recommendations for which are currently under development.[74] Although primarily targeted at MCI and early dementia, the workflow can occasionally be applied to patients in the moderate-to-severe stages of dementia according to clinician discretion and when a better differential diagnosis would affect patient care.

In conclusion, we envision that this diagnostic workflow will promote consistency in the diagnosis of neurocognitive disorders across European countries and facilitate a rational use of resources. Future steps will involve testing its acceptability and feasibility in the intended context of use of specialist outpatient services for patients with cognitive complaints (memory clinics), and the effects of its use on process outcomes (eg, patient journey, appropriateness of biomarker use, specialists' diagnostic confidence and accuracy, appropriateness of treatment plans), patient-related outcomes (eg, treatment-related adverse events), and appropriateness of use of resources.

Contributors

GBF and FN designed and conceptualised the study protocol, were the Principal Investigator and co-Principal Investigator, provided the structure of the manuscript, led the decision-making process of Delphi rounds, and contributed to drafting and revising the manuscript. GBF raised the funds for the project. CF was the project manager, and contributed to the decision-making process of Delphi rounds and manuscript writing. MCR and FM contributed to the decision-making process of Delphi rounds and manuscript writing. All authors acquired and interpreted the data and had access to all the data in the study. All authors contributed intellectual content, revised the manuscript, and agreed to submit the manuscript, including the revised versions.

Declaration of interests

DA has received research support or honoraria from Roche Diagnostics, Sanofi, and Eli Lilly; has served as a paid consultant for Roche Diagnostics and Takeda; and is a member of the Dementia Management steering committee for the European Association of Neurology. FA has acquired research support (for their institution) from the Italian Ministry of Health, AriSLA (Fondazione Italiana di Ricerca per la SLA), European Research Council, and Alzheimer's Research Foundation; and has served as a speaker for Biogen, Idec, Italfarmaco, Roche, and Zambon. BB has served as a consultant for PIAM; has a patent on neurophysiological markers and neurophysiological treatment approaches in Alzheimer's disease; and has participated on a data safety monitoring board or advisory board for Alector, UCB, Wave, AviadoBio, Lilly/Prevail, and Denali. SFC has received honoraria for lectures or presentations from Biogen, Roche, and Nutrucia, and has served as a consultant for Brain Control. CF has received funding through her institution from the Alzheimer's Association and Italian Ministry of Health. GBF has received funding through the Private Foundation of Geneva University Hospitals from APRA (Association Suisse pour la Recherche sur la Maladie d'Alzheimer), Fondation Segré, Ivan Pictet, Race Against Dementia Foundation, Fondation Child Care, Fondation Edmond J Safra, Fondation Minkoff, Fondazione Agusta, McCall Macbain Foundation, Nicole et René Keller, and Fondation AETAS; has received funding through the University of Geneva or Geneva University Hospitals for investigator-initiated sponsored studies from Roche, OM Pharma, Eisai, Biogen, and Novo Nordisk; has received funding for competitive research projects from EU-Horizon2020, Innovative Medicines Initiative (IMI), IMI2, Swiss National Science Foundation, and VELUX Foundation; and via their institution has served as a consultant or speaker for Biogen, Diadem, Roche, Novo Nordisk, and GE HealthCare. LF has acquired research support through his institution from Hector Foundation (FRAILBRAIN), EU-Horizon2020 (RECAGE, 2D-BioPAD), and EU-IMI2 (RADAR-AD); has received consultancy or speaker fees from Biogen, Eisai, Grifols, Neurimmune, Noselab, NovoNordisk, Roche, Schwabe, and TauRX; has served as an advisory board member for Avanir-Otsuka, Pharmatrophix, Forschungszentrum Jülich, Charité Berlin, Neurimmune, Neurokine Therapeutics, NSC Therapeutics, reMYND NV, Vivoryon, and European Alzheimer's Disease Consortium; and has served on the Alzheimer Europe Expert Advisory Panel (unpaid). VG was supported by the Swiss National Science Foundation (projects 320030_169876, 320030_185028 and IZSEZ0_188355), Velux Foundation (project 1123), Schmidheiny Foundation, and Aetas Foundation; and has received financial support for research or speaker fees through her institution from Siemens Healthineers, GE HealthCare, and Novo Nordisk. JG is an employee of Alzheimer Europe, which has received grants from the EU's Health, Horizon Europe, and Citizens, Equality, Rights and Values programmes, the Innovative Health Initiative, Joint Programme for Neurodegenerative Disease Research, and Luxembourg Fonds National de la Recherche; and has received sponsorship and support from AbbVie, Biogen, Eisai, Essity, Fujirebio, GE HealthCare, Grifols, Janssen, Lilly, MSD, Novo Nordisk, Nutricia, Prothena, Roche, and TauRx. OH has acquired research support (for their institution) from ADx, Avid Radiopharmaceuticals, Biogen, Eli Lilly, Eisai, Fujirebio, GE HealthCare, Pfizer, and Roche; and in the past 2 years has received consultancy or speaker fees from AC Immune, Amylyx, Alzpath, BioArctic, Biogen, Cerveau, Eisai, Eli Lilly, Fujirebio, Merck, Novartis, Novo Nordisk, Roche, Sanofi, and Siemens. AK has received through the National Institute of Mental Health, Neurology and Neurosurgery

grants from the National Brain Research Program, Hungary I, II (KTIA_NAP_13-1-2013-0001; 2017-1.2.1-NKP-2017-00002); and she is Secretary and Treasurer of the European, Middle East, and Africa Chapter of the International Society of Clinical Neurophysiology (unpaid). RPCK has received royalties from Hogrefe Test Publishing, Bohn Stafleu Van Loghum, LannooCampus Publishers, and Taylor & Francis; honoraria from Benecke Education Lecture and RINO Utrecht; has served as a consultant for University of Michigan Consultancy, Pearson Assessment, and Europees Fonds voor Regionale Ontwikkeling OP-Oost EU Grant Consultancy (fee paid to university). FM has received a speaker honorarium from Roche Diagnostics. SDM has received grants through her institution from the Italian Ministry of Health; and consulting fees, honoraria, or support for attending meetings from Eli Lilly, GE HealthCare, and Life Molecular Imaging. JTO has received academic support or grants from Avid-Lilly, Merck, and Alliance Medical; has received (for his institution) consulting fees from TauRx, Novo Nordisk, Biogen, Roche, Lilly, and GE HealthCare. SO has received support for attending meetings from PIAM, Alector, and MSD. PS has acquired research support through his institution from Novo Nordisk (co-chair of EVOKE programme), Toyama (Principle Investigator of phase 2b study), UCB (Principle Investigator of phase 1b study), AC Immune (Principle Investigator of phase 1b study), and Alzheon (Principle Investigator of phase 2a study); has served as a consultant for Immunobrain Checkpoint (paid to university); is a member of a data safety and monitoring board of a phase 3 study for AB Science; and is chair of the World Dementia Council (unpaid). WMvdF has conducted research programmes funded by ZonMW, Nederlandse Organisatie voor Wetenschappelijk Onderzoek, European Union–Seventh Framework Programme, European Joint Programme on Neurodegenerative Diseases, Alzheimer Nederland, Hersenstichting CardioVascular Onderzoek Nederland, Health~Holland, Topsector Life Sciences & Health, Stichting Dioraphte, Gieskes-Strijbis Fonds, Stichting Equilibrio, Edwin Bouw Fonds, Pasman Stichting, Alzheimer & Neuropsychiatrie Foundation, Philips, Biogen MA, Amprion, Novartis-NL, Life Molecular Imaging, Avid, Roche, Fujifilm, Eisai, and Combinostics. WMvdF holds the Pasman chair; is a recipient of ABOARD, which is a public–private partnership receiving funding from ZonMW (#73305095007) and Health~Holland, Topsector Life Sciences & Health (PPP-allowance; #LSHM20106), all funding is paid to her institution; she is a recipient of TAP-dementia, receiving funding from ZonMw (#10510032120003) in the context of Onderzoeksprogramma Dementie, part of the Dutch National Dementia Strategy; Gieskes Strijbis Fonds also contributes to TAP-dementia. WMvdF is a consultant for the Oxford Health Policy Forum community interest company, Roche, Eisai, and Biogen MA; has been an invited speaker at Boehringer Ingelheim, Biogen MA, Danone, Eisai, WebMD Neurology (Medscape), NovoNordisk, Springer Healthcare, and the European Brain Council; and has participated in advisory boards for Biogen MA, Roche, and Eli Lilly. FV has served as consultant for Biogen (payment to Maastricht University). MV is a recipient of ABOARD, which is a public–private partnership receiving funding from ZonMW (#73305095007) and Health~Holland, Topsector Life Sciences & Health (PPP-allowance; #LSHM20106); is a recipient of TAP-dementia, a ZonMw funded project (#10510032120003) in the context of the Dutch National Dementia Strategy; and is Chair of the Diagnostic Committee and Member of the Executive Committee of the European Society of Neuroradiology, which is an unpaid position. All other authors declare no competing interests.

Acknowledgments

LF and FJ were delegated from the European Alzheimer Disease Consortium; FV and MV from the European Association of Geriatric Psychiatry; KSF and FA from the European Academy of Neurology; SDM and VG from the European Association of Nuclear Medicine; DA and JTO from the European DLB Consortium; CB and AK from the Europe, Middle East, and Africa Chapter of the International Federation of Clinical Neurophysiology; TY and MWV from the European Society of Neuroradiology; SFC and RPCK from the Federation of the European Societies of Neuropsychology; BB and MO from the European FTD network; AH and AP-L from the International Federation of Clinical Chemistry; FBP and RV from the European Union of Medical Specialists. We acknowledge unrestricted grants from F Hoffmann-La Roche, Biogen International, Eisai Europe, Life Molecular Imaging, and OM Pharma Suisse. The funders had no role in the conception, design, and implementation of the project nor in data collection, data analysis, interpretation, or discussion of the results. Funders had no privileged access to the project's outputs at any stage.

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