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RESEARCH ARTICLE

European consensus for the diagnosis of MCI and mild dementia: Preparatory phase

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Abstract

Introduction: Etiological diagnosis of neurocognitive disorders of middle-old age relies on biomarkers, although evidence for their rational use is incomplete. A European task force is defining a diagnostic workflow where expert experience fills evidence gaps for biomarker validity and prioritization. We report methodology and preliminary results.

Methods: Using a Delphi consensus method supported by a systematic literature review, 22 delegates from 11 relevant scientific societies defined workflow assumptions.

Results: We extracted diagnostic accuracy figures from literature on the use of biomarkers in the diagnosis of main forms of neurocognitive disorders. Supported by this evidence, panelists defined clinical setting (specialist outpatient service), application stage (MCI-mild dementia), and detailed pre-assessment screening (clinical-neuropsychological evaluations, brain imaging, and blood tests).

Discussion: The Delphi consensus on these assumptions set the stage for the development of the first pan-European workflow for biomarkers' use in the etiological diagnosis of middle-old age neurocognitive disorders at MCI-mild dementia stages.

KEYWORDS
consensus, Delphi procedure, etiological diagnosis, imaging, major neurocognitive disorder, MCI, mild dementia – biomarker, neurocognitive disorders

Highlights

- Rational use of biomarkers in neurocognitive disorders lacks consensus in Europe.
- A consensus of experts will define a workflow for the rational use of biomarkers.
- The diagnostic workflow will be patient-centered and based on clinical presentation.
- The workflow will be updated as new evidence accrues.

1 | INTRODUCTION

Imaging and cerebrospinal fluid (CSF) biomarkers have radically changed the clinical approach to the disorders leading to cognitive and/or behavioral impairment.[1–3] Many of them are widely used in clinical practice, feeding the diagnostic pathway with morphological, neurophysiological, and molecular information. Magnetic resonance imaging (MRI) tools are routinely performed to measure regional atrophy and to detect cerebrovascular damage. [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET) allows the detection of suggestive patterns of hypometabolism associated with early synaptic and neuronal dysfunction.[4] Decreased β-amyloid 1-42(Aβ42) or Aβ42/Aβ40 ratio in cerebrospinal fluid (CSF) and increased retention of amyloid-PET tracer denote pathological amyloid deposition in the brain.[5] Increased CSF phosphorylated tau and tau-PET tracers accumulation denote tauopathy, particularly that associated with Alzheimer's disease (AD).[6,7] Dopamine transporter (DaT) imaging and myocardial scintigraphy with [^{123}I]-metaiodobenzylguanidine (MIBG) investigate the functional integrity of the nigrostriatal pathway[8] and postganglionic sympathetic heart terminals, respectively, potentially revealing the molecular imaging signature of Lewy body disorders.[9,10] Electroencephalography (EEG) can be abnormal in some encephalopathies and shows some characteristic patterns in rapidly progressive dementia and is paramount to disclose epileptic discharges in dementia-related epilepsy.[3] Last, polysomnography (PSG) detects the characteristic rapid eye movement (REM) sleep abnormalities of synucleinopathies.[11]

Available guidelines and recommendations supporting the diagnostic use of biomarkers focus mainly on individual biomarker performance and their role in specific diseases (Supplementary Tables S1 and S2, which is available online). The sparse evidence on their comparative and/or combined diagnostic utility[12] does not allow an integrated and sequential indication of biomarker use in the clinical setting, where several diagnostic options challenge the clinician. Furthermore, practical considerations (accessibility, waiting list, practicalities, local regulations, or national guidelines) or personal confidence often weigh

RESEARCH IN CONTEXT

1. **Systematic review**: In 2017, an international task force performed an extensive review of the state of maturity of biomarkers for the etiological diagnosis of neurocognitive disorders.[12] In 2020, the attempt by an Italian inter-societal working group to define the rational use of biomarkers for the etiological diagnosis of neurocognitive disorders was limited by the national context and small number of panelists.[13]
2. **Interpretation**: A task force appointed by eleven European scientific societies used the Delphi methodology, supported by a literature review, to define a workflow for the rational use of biomarkers in the etiological diagnosis of neurocognitive disorders in MCI and mild dementia stages.
3. **Future directions**: The workflow will promote consistency in diagnosing neurocognitive disorders across countries, and rational use of resources. The impact of the initiative will consist in preparing clinicians to work in the upcoming clinical context where etiological disease-modifying drugs will be available.

more than evidence-based considerations of effectiveness and utility in choosing biomarkers, leading to significant heterogeneity of health care in Europe.[12]

In 2020, an Italian task force of seven dementia experts representing the five pertinent national scientific societies (neurology, neuroradiology, clinical chemistry and laboratory medicine, psychogeriatrics, and nuclear medicine) developed a consensus algorithm to guide the choice of biomarkers for the etiological diagnosis of mild cognitive impairment (MCI), maximizing positive and negative predictive values to avoid unnecessary investigations.[13] The main limitation of that initiative regarded the absence of a systematic literature review of the evidence on biomarkers' accuracy to support the choice, the national context, the small number of panelists, and the target restricted to patients with cognitive symptoms.

To overcome those limitations, eleven European scientific societies and organizations and a European patient advocacy association have combined efforts to define a European workflow for a biomarker-based etiological diagnosis of the most frequent forms of neurocognitive disorders of middle-old age at the MCI and mild dementia stages, leveraging on a Delphi method, supported by an up-to-date literature review.[14,15]

In this paper, we describe the preparatory phase of the initiative, that is, the methodological and content fundamentals including (1) the selection of the panel members, (2) the systematic review of studies assessing the accuracy of biomarkers, (3) the procedure of the Delphi rounds, and (4) clinical context of development and use of the diagnostic consensus, as derived from the first Delphi round.

2 | METHODS

The Delphi method is a group facilitation technique used to achieve a shared opinion or decision by surveying a panel of experts (i.e., the panelists) through a series of structured questionnaires, commonly referred to as rounds.[16–19] In this project, we applied the modified Delphi method.[20] Briefly, Delphi questions were drafted by the facilitators and submitted to an external reviewer who assessed whether the questions were sufficiently clear, neutral, informative, and complete. Using a web-based platform, panelists were sent the revised questions with instructions to respond on each topic based on their expert opinion, experience, and evidence from the literature (Figure 1). All responses had to be justified. We allowed panelists to abstain from voting when the topic of the question was outside their area of expertise. We defined an a priori threshold of 70% of non-abstaining voting panelists for agreement. When a question needed re-discussion, an absolute majority (50%+1) was sufficient for agreement.

2.1 | The task force

The project task force consisted of three coordinated working groups: the executive board (EB), the Panel, and the Scientific Advisory Board (SAB; details in Table 1). The EB consisted of Delphi facilitators and an "external" reviewer, supervising the procedure. The Panel involved two delegates for each of eleven European scientific societies involved in the diagnosis/treatment of neurocognitive disorders. A patient advocate association (Alzheimer Europe) joined the initiative for its advising competence. Thus, the Panel consisted of 23 experts, including 22 respondents and one consultant, who reviewed the decision-making process on behalf of patients. Five world-renowned experts in the field of dementia made up the SAB. The SAB's role was to provide oversight of the entire process and intervene in any high-level conflicts where the panel fails to reach consensus.

2.2 | Systematic review of accuracy studies

To corroborate this Delphi procedure, we performed a literature review according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[21]

2.2.1 | Search strategy

We updated the literature review on biomarker accuracy performed during the Geneva Initiative for the Alzheimer's Disease Biomarker Roadmap[12] by performing a research of the Medline bibliographic database from January 2017. The search strategy used the PICO methodology (population, intervention, comparator, and outcome) considering only the terms "population" and "intervention" to maximize the likelihood of identifying relevant studies.[22] We considered only original studies published in English, excluding reviews, case reports,

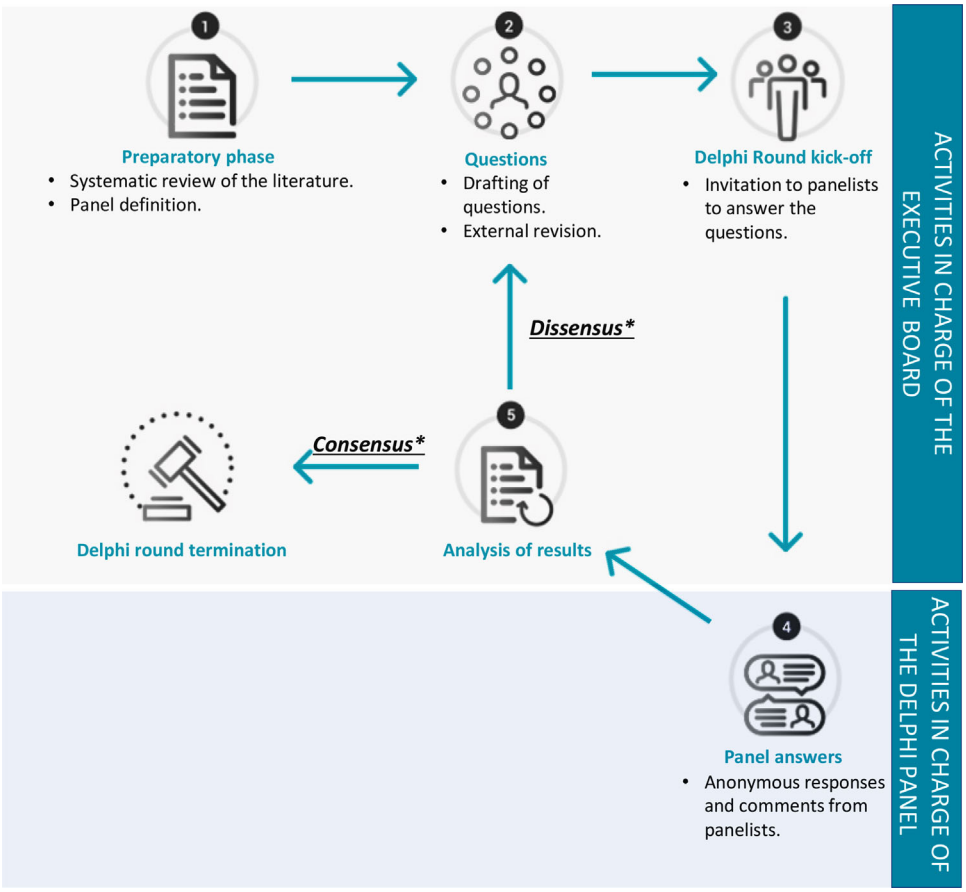

FIGURE 1 The Delphi method. The figure summarizes the modified Delphi approach applied in this study. In the preparatory phase, the executive board (EB) contacted European scientific societies and organizations and reviewed the scientific literature on the accuracy of biomarkers in the diagnostic work-up of patients with MCI. The EB finalized the questions, which, after approval by the external auditor, were sent by e-mail to the panelists. The answers were analyzed qualitatively and statistically. A consensus was achieved when the agreement was 70% or higher; else, the question was discussed in a further round. In the event of a re-discussion of the question, consensus is reached with an agreement of 50% + 1.

and guidelines. Search strings were harmonized across biomarkers and diagnoses (Supplementary Table S3).

The literature review was conducted in two subsequent stages. Strings built on the keyword "MCI" were launched on July 1, 2020. Careful analysis revealed that the resulting studies mainly referred to the prodromal phase of AD. Hence, in October 2020, we expanded the literature search to the terms "Lewy body", "frontotemporal lobe degeneration OR FTLD" and "primary progressive aphasias OR PPA". At the same time, we extended the search to EEG and PSG.

2.2.2 | Study selection

Titles and abstracts were screened, and potentially relevant studies were then examined in detail according to the following criteria: (1) minimum sample size of 50 MCI patients, (2) minimum follow-up of 3 years, (3) conversion to dementia or pathology as gold standard, (4) data concerning critical outcome measures, for example, sensitivity, specificity, accuracy, positive/negative predictive value, or positive/negative likelihood ratios. If not immediately available, confidence intervals were computed whenever possible. In less common disorders (i.e., dementia with Lewy bodies – DLB, FTLD, PPA), we accepted (1) smaller sample sizes ($n > 20$), (2) cross-sectional design, and (3) either clinical or biomarker-based diagnosis as the reference standard. This choice was motivated by the limited number of prospective studies with suitable sample sizes in these disorders, although we are aware of the higher risk of bias.

2.2.3 | Data extraction and quality assessment

Six reviewers, that is, CF, VN (researchers), FM, MCR (neurologists), and SO, FG (geriatricians), independently extracted several variables, namely number and diagnosis of enrolled patients, study design, details on technical execution and performance of the biomarkers, and gold/reference standard. Quality of evidence was rated using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2).[23] Raters were trained in QUADAS-2 and had fine-tuning methodological meetings to ensure uniformity and reproducibility of data extraction. Data were recorded in an Excel spreadsheet, modified from.[24]

TABLE 1 The task force for the European Inter-Societal Consensus on the biomarker-based diagnosis of MCI and mild dementia

The executive board		
Name	**Specialty**	**Capacity**
Giovanni B FRISONI	Neurology	Principal Investigator, Delphi facilitator
Flavio NOBILI	Neurology	Principal Investigator, Delphi facilitator
Cristina FESTARI	Psychology	Project manager, Delphi facilitator
Matteo COTTA RAMUSINO	Neurology	Delphi facilitator
Federico MASSA	Neurology	Delphi facilitator
Stefania ORINI	Geriatrics	Delphi facilitator
Wiesje M VAN DER FLIER	Psychology	External reviewer
The panel		
Representants	**Scientific society**	**Capacity**
1. Lutz FROELICH 2. Frank JESSEN	EADC	1. Chairperson 2. Vice chairperson
1. Frans VERHEY 2. Mathieu VANDENBULCKE	EAGP	1. Ordinary member 2. Ordinary member
1. Kristian S. FREDERIKSEN 2. Federica AGOSTA	EAN	1. Co-chairperson of the Dementia Panel 2. Co-chairperson of the Neuroimaging Panel
1. Silvia MORBELLI 2. Valentina GARIBOTTO	EANM	1. Chairperson of the Neuroimaging Committee 2. Member of the Neuroimaging Committee
1. Dag AARSLAND 2. John T O'BRIEN	E-DLB	1. Chairperson 2. Steering Committee Member
1. Claudio BABILONI 2. Anita KAMONDI	IFCN	1. Co-chairperson of Special Interest Group 2. Executive Committee member
1. Tarek YOUSRY 2. Meike VERNOOIJ	ESNR	1. Vice-President 2. Chairperson of the Diagnostic Neuroradiology Committee
1. Stefano CAPPA 2. Roy P.C. KESSELS	FESN	1. Past President 2. Scientific Advisory Board
1. Barbara BORRONI 2. Markus OTTO	FTD	1. Principal Investigator 2. Principal Investigator
1. Alexander HALIASSOS 2. Armand PERRET-LIAUDET	IFCC	1. Member of the executive board 2. Chairperson of Committee on Proficiency Testing
1. Francesca B PIZZINI 2. Ritva VANNINEN	UEMS	1. Secretary of the Division of Neuroradiology 2. Ordinary member
1. Jean GEORGES	Alzheimer Europe[a]	1. Executive Director
The Scientific Advisory Board		
Mercè BOADA ROVIRA	Craig RITCHIE	Philip SCHELTENS
Bruno DUBOIS	Oskar HANSSON	

Note: The table lists all the actors of the initiative, that is, members of the executive board (EB), the panel of experts delegated by the scientific societies and organizations and the Scientific Advisory Board (SAB).
Abbreviations: EADC, European Alzheimer Disease Consortium; EAGP, European Association of Geriatric Psychiatry; EAN, European Academy of Neurology; EANM, European Association of Nuclear Medicine; E-DLB, European DLB Consortium; ESNR, European Society of Neuroradiology; FESN, Federation of the European Societies of Neuropsychology; FTD, European FTD network; IFCC, International Federation of Clinical Chemistry – Education and Management Division; IFCN, Europe, Middle East and Africa Chapter of the International Federation of Clinical Neurophysiology; UEMS, European Union of Medical Specialists.
[a]Consultant.

2.3 | The first Delphi round

The EB defined 10 questions (Figure 3), namely critical assumptions to define the clinical context of the diagnostic workflow, for discussion by panelists in the first Delphi round. These assumptions mainly concerned the project aim, the target clinical population, the clinical context of use of the workflow, and the first level of the diagnostic workup for people with cognitive and/or behavioral complaints. Other assumptions covered the theoretical setting of the diagnostic workflow, that is, definition of diseases and respective diagnostic criteria,

TABLE 2 Delphi panelists' profiles

Biomarker frequency of use and type of assessment	n of responders *	Estimation of monthly cases % (Range)	Estimation of monthly cases Median (±IQR)	Frequency of use, % of responders' answers † Never	Rarely	Moderately	Frequently	Always
MRI	15	60-100	100 (8)	7%				93%
Traditional qualitative reporting	15	0-100	50 (100)	27%	13%	13%		47%
Visual rating scales	15	0-100	100 (50)	7%	20%	7%		67%
Hippocampal volumetry	15	0-100	5 (38)	40%	20%	20%		20%
FDG-PET	13	0-95	30 (55)	8%	23%	38%	15%	15%
Traditional qualitative reporting	13	0-100	40 (95)	15%	15%	23%	8%	38%
Semi-quantitative metrics	13	0-80	0 (0)	77%			15%	8%
Voxel-based assessment	13	0-100	1 (30)	46%	15%	15%		23%
Amyloid PET	13	0-30	5 (10)	31%	54%			15%
Traditional qualitative reporting	13	0-100	10 (100)	31%	23%	8%		38%
Semi-quantitative metrics	13	0-100	0 (10)	54%	23%		8%	15%
Voxel-based assessment	13	0-100	0 (0)	77%			8%	15%
CSF biomarkers	11	5-80	60 (48)	9%	36%	36%		18%
tau PET	13	0-60	0 (0)	77%			15%	8%
Traditional qualitative reporting	13	0-100	0 (0)	85%				15%
Semi-quantitative metrics	13	0-100	0 (0)	92%				8%
EEG	12	0-90	5 (18)	42%	33%	8%	8%	8%
Traditional qualitative reporting	12	0-100	5 (68)	42%	17%	8%	8%	25%
Quantitative metrics	12	0-10	0 (3)	75%				25%
Polysomnography	13	0-20	4(5)	30%	60%			10%
DaT SPECT/PET	13	0-30	5(5)	8%	69%			23%
Traditional qualitative reporting	13	3-100	5 (55)	62%		8%	8%	23%
Semi-quantitative assessment	13	0-100	3 (20)	46%	23%		15%	15%
MIBG cardiac scintigraphy	12	0-5	0 (1)	62%		38%		
Traditional qualitative reporting	12	0-100	0 (16)	58%	17%		8%	17%
Semi-quantitative assessment	10	0-100	0 (11)	67%		8%	8%	17%

*not responders were due to questions not pertinent.

Note: Expertise with the use of biomarkers for the etiological diagnosis of neurocognitive disorders in their clinical practice.
Abbreviations. CSF, cerebrospinal fluid; DaT, Dopamine transporter; EEG, electroencephalogram; FDG,18F-fluorodeoxyglucose; IQR, range inter quartile; MCI, mild cognitive impairment; MIBG, [123I]-metaiodobenzylguanidine; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single photon emission computed tomography.
[a]Not responders were due to questions not pertinent.
[b]The frequency of use was operationalized as follows: estimated monthly cases of 0% = never; between 1%–19% = rarely; 20%–59% = regularly; 60%–79% = frequently; above 80% = always.

classification of biomarkers, and role of logistic-economic factors. The first round was launched on November 25, 2020.

3 | RESULTS

3.1 | Selection of the Delphi panel members

The panel consists of specialists on behalf of different scientific societies, that is, five neurologists, four psychiatrists, two geriatric psychiatrist, four neuroradiologists, two experts in clinical chemistry, two nuclear medicine physicians, two clinical neurophysiologists, and a neuropsychologist. Ten experts are clinicians, nine are physicians working in diagnostic departments (with radiological, nuclear medicine, or laboratory expertise), and three cover both fields. All have a long professional experience (median ± interquartile range, IQR, years: 24 ± 13 for clinicians, and 21 ± 12 for the other physicians). Most clinicians stated to use biomarkers for diagnostic purposes in their clinical practice routinely. Table 2 shows that the only biomarker used systematically is MRI (93% of clinicians), mainly by standardized visual scales (e.g., medial temporal lobe atrophy scales in 67%), while CSF biomarkers and FDG-PET are routinary for 90% and 68% of clinicians, respectively. Most clinicians estimated a less frequent use of DaT imaging (69%), polysomnography (60%), amyloid-PET (54%), cardiac MIBG-scintigraphy (38%), and electroencephalography (33%). Seventy-seven percent of clinicians never used the recently developed tau-PET tracers for clinical purposes.

3.2 | Systematic review of studies of accuracy

A total of 2200 papers were identified and screened for subsequent processing. After excluding duplicate papers and those not addressing biomarkers performance, 859 papers fulfilling the inclusion criteria were assessed in detail (Supplementary Figure S1). Among them, 692 were excluded because they reported: (1) qualitative data on biomarkers performance, mostly obtained by correlation analyses or comparisons with control groups or (2) accuracy values calculated

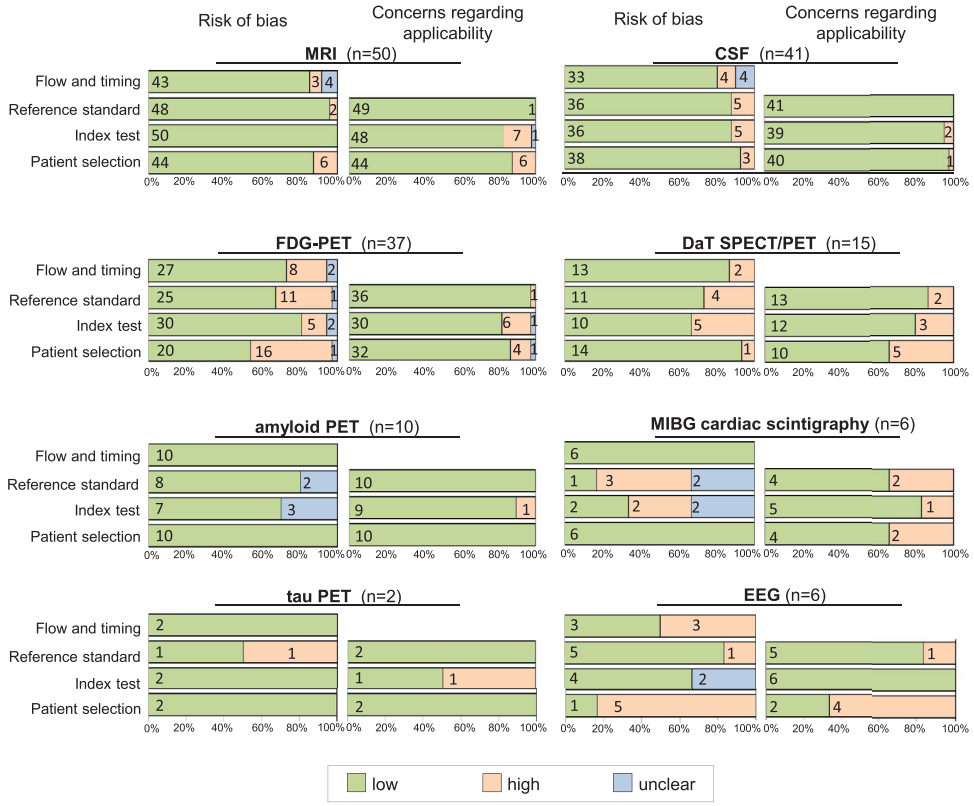

FIGURE 2 Systematic review of the literature: quality assessment according to the QUADAS-2 criteria. The methodological quality of scientific articles was assessed for each biomarker according to the QUADAS-2 criteria. The QUADAS-2 consists of four key domains covering patient selection, index test, reference standard, and patients flow through the study and timing of the index test(s) and reference standard ("flow and timing"). Each domain is assessed in terms of the risk of bias and the first three are also assessed in terms of concerns regarding applicability in the routine clinical context. Bar graphs summarize the number and percentage of articles with low, high or unclear ratings in each domain. For each study of test accuracy, the QUADAS-II evaluates whether the biomarker (i.e., index test): (1) was interpreted knowing the result of the gold standard (diagnosis at FU or pathology) or the reference standard (biomarker-based diagnosis or clinical diagnosis) and (2) it was quantified using standard metrics and avoiding recursive methodology.

using multifactorial models from which the exclusive weight of the analyzed biomarker was not obtainable. The remaining 167 provided validated measures of biomarker diagnostic accuracy compared with a gold/reference standard or in predicting progression or conversion of MCI to the dementia stage (i.e., AD, DLB, and FTLD). Fifty studies provided accuracy values for MRI, 41 for CSF, 37 for FDG-PET, 15 for DaT-imaging, 10 for amyloid-PET, 2 for tau-PET, and 6 for myocardial MIBG-scintigraphy and EEG, respectively.

The QUADAS-2 assessment is summarized in Figure 2 and appendix (file: QUADAS-II_ListRef.xlsx, cloud-based repository: 10.17632/8sxf8tvwgm.1). Quality of evidence was strong in 73 studies (43%), without risk of bias or concerns about applicability in all domains. The amyloid-PET and MRI performance findings were the most robust and generalizable (60% and 62% of studies, respectively). These findings showed that semi-quantitative amyloid-PET assessment performed with an average accuracy of 74% (range: 57%–84%) in predicting clinical progression in 597 MCI patients, whereas quantitative MRI assessment performed with an average accuracy of 78% (range: 68%–98%) in predicting progression in 5727 MCI patients. The number of studies considered methodologically acceptable amounted to 94 (56%), including those with minimal risks of bias or applicability. The main methodological limitations were related to bias in (1) patient selection (i.e., lack of consecutive or randomized selection of subjects, use of a case-control design, or inappropriate exclusions, $n = 31$), (2) reference standard (i.e., either inaccurate to classify the target condition or interpreted with knowledge of index test results, $n = 26$), and (3) index test (i.e., interpreted with knowledge of the results of the reference standard or not a priori defined pathological cutoff; $n = 21$). Concerns regarding applicability were mostly related to non-routinary methods ($n = 22$) and only marginally to the chosen reference standard ($n = 10$). Ten studies reported insufficient data about the time interval of data acquisition.

3.3 | Results of the first Delphi round

Consensus was reached for 8 out of 10 questions (Figure 3). The panelists agreed to define a workflow for the rational use of biomarkers in the etiological diagnosis of middle-old age neurocognitive disorders at MCI and mild dementia stages, also labeled as mild or major

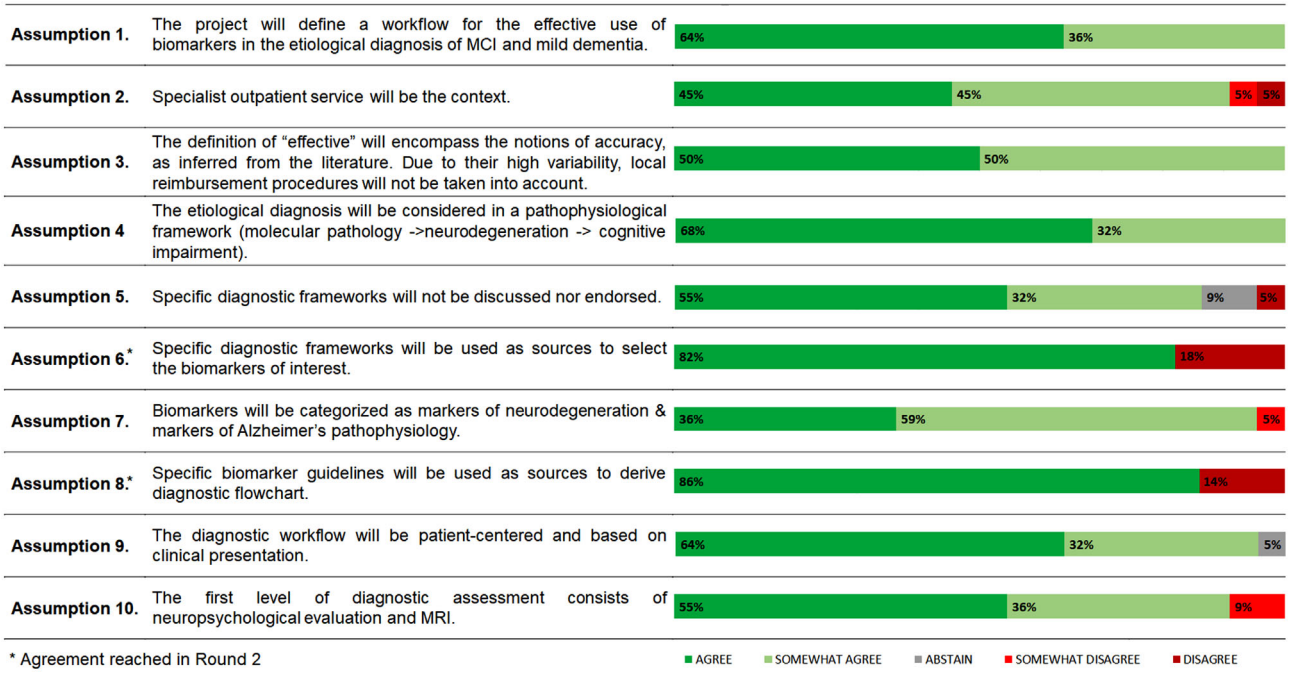

FIGURE 3 Definition of the clinical context. In the first Delphi round, panelists answered 10 assumptions to define the clinical context of developing the diagnostic workflow. Figure reports questions and corresponding percentage of agreement. Consensus is achieved when the sum of "agree" and "somewhat agree" is 70% or higher. Agreement was reached in a single round for all assumptions except #6 and #8 which required a second round.

neurocognitive disorder according to Diagnostic and Statistical Manual of mental disorders (DSM5; assumption 1; votes: 14[agree] – 8[somewhat agree] – 0[somewhat disagree] – 0[disagree]- 0[abstain]). Specialist outpatient service with a specific interest in neurocognitive disorders was voted as the most appropriate context for using the workflow. This designation was preferred to "memory clinic" to include all health care structures dealing with patients with cognitive and/or behavioral presentations (assumption 2; votes: 10–10–1–1–0). The first level of diagnostic assessment consisted of clinical examinations, blood tests, extensive neuropsychological evaluation, and morphological imaging (assumption 10; votes: 12–2–0–2–0). This initial evaluation is imperative to define a clinical-brain morphological profile (syndromic level) and then to proceed in the workflow to detect the underlying etiology when an organic cause is suggested (assumption 9; votes: 14–7–0–0-1). The specific diagnostic categories addressed by the workflow and their clinical profiles were designed according to updated diagnostic criteria (assumption 6; agreement reached in Round 2: 18–0–0–4–0; references listed in Supplementary Table S1). Assumption 4 stated that neurocognitive disorders reflect the neuronal damage resulting from the underlying molecular pathology (votes:15–7–0–0–0). Diagnostic biomarkers were thus categorized into two main groups: (1) markers of pathophysiology (amyloid-PET, tau-PET, CSF Aβ42 and Aβ42/40 ratio, and CSF phospho-tau) and (2) markers of neuronal damage/neurodegeneration (morphological MRI, FDG-PET, EEG, DaT-imaging, [123I]-MIBG cardiac scintigraphy, CSF total tau) (assumption 7; votes: 8–13–0–1–0). We are aware that this reductionist approach misses the richness of the information potentially provided by most of the neurodegeneration biomarkers, that might be conceived as an intermediate between pathophysiology and neuronal damage. This is especially evident for FDG-PET, exploring the astrocyte-synapsis functional unit, EEG that probes (de)synchronization of cortical pyramidal neurons and related functional network organization, emerging CSF biomarkers (i.e., synaptic or blood barrier dysfunction), and some MRI modalities. In this line, even a revisitation of the ATN system has been claimed to increase the accuracy in staging the disease course.[25] However, the aim of our initiative is exquisitely applicative, and we do not wish to enter this debate. When answering assumption 7, some panelists stressed the importance of potentially upcoming markers (e.g., neurofilament light chain measurement in CSF or plasma, fluid and PET markers of inflammation or synaptic dysfunction, CSF progranulin, other blood biomarkers) or technologies (arterial spin labeling MRI perfusion and resting-state functional MRI methods, real-time quaking-induced conversion (RT-QuIC)), even if not included in the original assumption. The panelists defined the best published guidelines or recommendations for choosing biomarkers (assumption 8; agreement reached in Round 2: 19–0–0–3–0; selected references listed in Supplementary Table S2). They agreed the information provided by biomarkers should be interpreted by physicians according to the diagnostic framework they are used to (assumption 5; votes:12–7–0–1-2); in fact, the panel neither discussed nor endorsed any specific diagnostic context. Noteworthy, it was specified that the definition of the diagnostic workflow should not consider local reimbursement procedures, costs, or availability of biomarkers, as they constantly update over time (assumption 3; votes:11–11–0–0–0).

4 | DISCUSSION

This work describes the preparatory phase and preliminary results of a European Delphi consensus for the biomarker-based etiological diagnosis of neurocognitive disorders of middle-old age at MCI-mild dementia stages. These include panelists' selection, literature review, and definition of the appropriate clinical context for the workflow use.

Biomarkers are widely used in clinical practice for diagnostic purposes, based on their analytic validity and evidence of clinical validity, even if still incomplete. However, choosing the most rational biomarkers for a specific clinical situation requires evidence of both diagnostic and added informative value. The latter depends on the prior probability, consisting of other already available information and modulated by the patient's age. Evidence of granularity at this level would require studies of unfeasible size and is not available for most biomarkers used in medicine, including those for neurodegenerative diseases.[12] On the other hand, daily clinical practice allows experts to derive unstructured information from patient care to supplement available evidence. For this purpose, the iterative process behind the Delphi approach is particularly suited to gaps scientific evidence and define a diagnostic consensus.[16–19]

In any Delphi procedure, the choice of the panel members is critical and a potential source of bias, that is, results may be skewed toward a particular outcome related to the panelists' primary area of expertise.[26–28] To prevent this, we chose a priori the medical specialties dealing with diagnostic biomarkers and gave two-panel seats to each of the pertinent scientific societies. This balanced approach equally represented all specialties, reduced the weight of idiosyncratic votes, and allowed a sufficient number of participants to guarantee stable results.[29–33] As an intrinsic limitation, each panelist may be an expert of the pertinent biomarker of interest and little of the others. This potential issue is mitigated by providing all panelists with the pertinent literature review in all the Delphi rounds and giving them the option to abstain.

In the first Delphi round, the panelists agreed that patients with mild cognitive or behavioral complaints referred to specialist outpatient services should receive, if possible, an accurate etiological diagnosis. The implications are twofold. First, panelists implicitly endorsed the concept that assessment of the specific disease substrate is useful regardless of the availability of drug treatments. This reveals interest in forthcoming treatments, namely disease-modifying drugs targeting those specific proteinopathies that cause neurodegeneration (e.g., anti-amyloid, anti-tau, and anti-α-synuclein agents) and requiring precise molecular profiling.[34] As a striking example, the absence of the amyloid profile as an inclusion criterion was among the factors contributing to the failure of some clinical trials of anti-amyloid drugs in AD.[35] Second, panelists endorsed the notion that an etiological diagnosis is valuable already in current clinical practice. Patients and their caregivers deserve to be informed about the cause of symptoms. This falls under the concept of "value of knowing," which has several and pivotal implications.[36] An etiologic diagnosis reduces uncertainty, improves patient and caregivers' well-being, and may be relevant for assessing the risk of disease inheritance and informed decision-making, such as planning for health, legal, and financial decisions. In fact, prognosis differs significantly among different etiologies.[37] Furthermore, an etiological diagnosis ensures a more appropriate treatment plan. The currently licensed drugs (i.e., acetylcholinesterase inhibitors and memantine) is indeed indicated and effective in AD and DLB but can be detrimental to cognition in the behavioral variant of FTD,[38] while memantine is licensed in AD but poorly effective in DLB.[39]

The Delphi panel endorsed an approach focused on the clinical profile that better reflects the real-world context for which the workflow is intended and allows for ease of use in daily practice. This attempts to overcome the limitations of the disease-centered approach used by previous recommendations that focused on the most effective biomarker(s) for each specific disease, that is an abstraction from the clinical phenotype, often posing multiple diagnostic hypotheses.[13,40] In fact, different pathological conditions may be responsible for largely overlapping clinical pictures, as well as a single disease can present with different clinical phenotypes, raising the real problem, that is, the differential diagnosis. Neglecting the clinical profile prevents the formulation of plausible alternative diagnoses if the first-choice biomarker turns out to be negative, prematurely halting the diagnostic workflow. Moreover, it precludes proper estimation of the incremental diagnostic value of the biomarker, which depends on the a priori diagnostic probability that the clinical profile helps to assess.

Intending to ensure fast workflow implementation in clinical practice, the panel agreed to consider only those biomarkers already in a more advanced stage of validation and mostly available while remaining open to future updates based on upcoming markers or technological innovations. Although aware of its incomplete maturity compared with other biomarkers, the panel suggested including tau-PET (e.g., the tracer already commercially available) because it is supported by growing relevant evidence.[7] Hence, the workflow development will be substantially driven by the current availability of amyloid and tau biomarkers and will focus on 'pure' pathologies, while other proteinopathies such as α-synuclein and TDP-43 inclusions, although not rarely co-occurring, may be overlooked. Specific biomarkers of these proteinopathies, when widely available soon, could pave the way for the diagnosis of mixed pathologies and fully personalized diagnoses and treatments.

Finally, the panel decided that the diagnostic workflow should not consider local factors, such as accessibility of procedures and reimbursement policy, which often weigh more heavily in selecting biomarkers than their diagnostic accuracy[11] and hinder optimal patient management.

The panel decisions reached during the first Delphi round represent the basic assumptions on which the diagnostic workflow will be built. Taking advantage of the iterative process of the Delphi procedure and fed with updated literature on the diagnostic accuracy of biomarkers, the panel will develop a workflow assuming that up to three waves of diagnostic investigations may be needed to achieve a diagnosis, mimicking clinician's diagnostic reasoning and current memory clinic practices. In fact, the choice of the first-line biomarker will depend on syndromic profiles, defined by clinical and neuropsychological features and MRI findings. The choice of the second-line biomarker

will take into account syndromic profiles and the results of the first-line biomarker.

Although the Delphi procedure is widely used to establish clinical recommendations when empirical scientific evidence is insufficient, it is not devoid of limitations. Response bias can be related to the mix of panel expertise, as mentioned above, and to implicitly suggestive wording of the questions. The mitigation actions we undertook were to appoint experts from all disciplines involved in clinical decision-making and appoint an external expert in the field who reviewed the questions before they were submitted to the panel. A simple majority for convergence (>50% of the panel) may hide important disagreement. In this case, the mitigation action we will undertake was to set a strict majority threshold of 70% in the first place, which will be relaxed to 50% only after failing to achieve majority.

The results of the first Delphi round described here represent also the first European level consensus on the proper context of use of biomarkers in clinical practice, the target clinical population, and the first level of the diagnostic workup. We acknowledge the workflow may require some adjustments in the future to be implemented in the local clinical routine. However, the availability of an agreed diagnostic workflow at the European level will provide physicians with an ideal reference standard, and scientific societies and regulators with a comprehensive and integrated framework for rediscussing reimbursement policies.

To sum up, a rigorous evidence-to-decision approach, based on systematic literature review and Delphi consensus procedure, will lead a multidisciplinary group of European experts to define the first diagnostic workflow on the rational use of biomarkers for the etiological definition of neurocognitive disorders, moving from the patient's clinical profile and disregarding logistic factors.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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