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Special Article

Updated Italian intersocietal recommendations for the appropriate use of anti-amyloid monoclonal antibodies in Alzheimer's disease

Alberto Benussi [a,b,*], Federica Agosta [c,d,e], Luisa Agnello [f,g], Alba Rosa Alfano [h], Mattia Altini [i,j], Antonio Antico [k], Stefania Basilico [l,m,n], Giuseppe Bellelli [o,p], Laura Bonanni [q], Gabriella Bottini [l,m,n], Marco Bozzali [r,s], Ovidio Brignoli [t], Giuseppe Bruno [u], Annachiara Cagnin [v,w], Sonia Francesca Calloni [x], Stefano F. Cappa [y,z], Filippo Caraci [aa,bb], Diego Cecchin [w,cc], Marcello Ciaccio [f,g], Sirio Cocozza [dd], Mirco Cosottini [ee,ff], Diego De Leo [gg,hh,ii], Andrea Falini [e,x], Lorenzo Gaetani [jj], Nicoletta Gandolfo [kk], Fabio Gotta [ll,mm], Raffaele Lodi [nn,oo], Giancarlo Logroscino [pp,qq], Elena Marcello [rr], Camillo Marra [ss,tt], Walter Marrocco [uu], Silvia Morbelli [vv,ww], Patrizia Mecocci [xx,yy], Enrico Mossello [zz], Lorenzo Palleschi [h], Pasquale Palumbo [aaa], Leonardo Pantoni [bbb,ccc,ddd], Lucilla Parnetti [jj], Luca Roccatagliata [eee,fff], Sandro Sorbi [ggg,hhh,iii], Patrizia Spadin [jjj], Alessandra Splendiani [kkk,lll], Alessandro Tessitore [mmm], Andrea Ungar [zz], Giuseppe Zappalà [nnn], Alessandro Padovani [ooo,ppp,qqq,rrr]

[a] *Neurology Unit, Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy*
[b] *Neurology Clinic, Department of Medicine, Surgery and Health Sciences, Azienda Sanitaria Universitaria Giuliano Isontina, Trieste, Italy*
[c] *Neuroimaging Research Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy*
[d] *Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy*
[e] *Vita-Salute San Raffaele University, Milan, Italy*
[f] *Department of Biomedicine, Neurosciences and Advanced Diagnostics, Institute of Clinical Biochemistry, Clinical Molecular Medicine, and Clinical Laboratory Medicine, University of Palermo, Palermo, Italy*
[g] *Department of Laboratory Medicine, University Hospital "Paolo Giaccone", Palermo, Italy*
[h] *Unit of Geriatrics, Medical Department, San Giovanni-Addolorata Hospital, Rome, Italy*
[i] *Modena Local Health Authority (Azienda USL Modena), Modena, Italy*
[j] *Italian Society of Leadership and Management in Medicine (SIMM), Rome, Italy*
[k] *Department of Laboratory Medicine, Hospital "Ca' Foncello", Treviso, Italy*
[l] *Cognitive Neuropsychology Centre, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy*
[m] *Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy*
[n] *NeuroMi - Milan Center for Neuroscience, Milan, Italy*
[o] *School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy*
[p] *Acute Geriatric Unit, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy*
[q] *Department of Medicine and Aging Sciences, "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy*
[r] *"Rita Levi-Montalcini" Department of Neuroscience, University of Torino, Turin, Italy*
[s] *Neurology Unit 2U, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Turin, Italy*
[t] *Italian College of General Practitioners and Primary Care Professionals (SIMG), Florence, Italy*
[u] *Department of Human Neuroscience, Sapienza University of Rome, Rome, Italy*
[v] *Department of Neuroscience, University of Padova, Padova, Italy*
[w] *Padova Neuroscience Center, University of Padova, Padova, Italy*
[x] *Neuroradiology Unit & CERMAC, IRCCS Ospedale San Raffaele, Milan, Italy*
[y] *IUSS Cognitive Neuroscience (ICoN) Center, University Institute of Advanced Studies IUSS, Pavia, Italy*

Abbreviations: AD, Alzheimer's disease; APOE, Apolipoprotein E; ARIA, Amyloid-related imaging abnormalities; ARIA-E, Amyloid-related imaging abnormalities with edema/effusion; ARIA-H, Amyloid-related imaging abnormalities with haemorrhage/haemosiderin; CDCD, Centre for Cognitive Disorders and Dementia; CDR, Clinical Dementia Rating; CDR-SB, Clinical Dementia Rating sum of boxes; CE-IVDR, European in vitro diagnostic regulation; CSF, Cerebrospinal fluid; DMT, Disease-modifying therapy; EMA, European Medicines Agency; EPA, Italian Expert Panel on Alzheimer; EPA2, Second Italian Expert Panel on Alzheimer; GRE, Gradient echo (T2*-weighted MRI sequence); MCI, Mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MRI, Magnetic resonance imaging; PDTA, Diagnostic and Therapeutic Care Pathways (Percorso Diagnostico-Terapeutico Assistenziale).

* Corresponding author at: Department of Medical, Surgical and Health Sciences, University of Trieste, Strada di Fiume, 447 34149 Trieste, Italy.
E-mail address: alberto.benussi@units.it (A. Benussi).

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[z] IRCCS Istituto Auxologico Italiano, Milan, Italy
[aa] Department of Drug and Health Sciences, University of Catania, Catania, Italy
[bb] Oasi Research Institute-IRCCS, Troina, Italy
[cc] Nuclear Medicine Unit, Department of Medicine (DIMED), University Hospital of Padova, Padova, Italy
[dd] Neuroradiology Unit, University Hospital "Federico II", Naples, Italy
[ee] Neuroradiology Unit, Department of Translational Research on New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy
[ff] Neuroradiology Unit, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy
[gg] Australian Institute for Suicide Research and Prevention, Griffith University, Nathan, QLD, Australia
[hh] Slovene Centre for Suicide Research, University of Primorska, Koper, Slovenia
[ii] De Leo Fund, Padova, Italy
[jj] Section of Neurology, Department of Medicine and Surgery, University of Perugia, Perugia, Italy
[kk] Dipartimento Immagini, SC Radiologia, Ospedale Villa Scassi - IRCCS AOM, Genova, Italy
[ll] Unit of Medical Genetics, IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[mm] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Health (DINOGMI), University of Genova, Genoa, Italy
[nn] Functional and Molecular Neuroimaging Unit, IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy
[oo] Department of Biomedical and Neuromotor Sciences (DIBINEM), University of Bologna, Bologna, Italy
[pp] Center for Neurodegenerative Diseases and the Aging Brain, University of Bari "Aldo Moro", Tricase-Lecce, Italy
[qq] Department of Translational Biomedicine and Neuroscience (DiBraiN), University of Bari "Aldo Moro", Bari, Italy
[rr] Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti", University of Milan, Milan, Italy
[ss] Memory Clinic, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy
[tt] Department of Psychology, Catholic University of the Sacred Heart, Milan, Italy
[uu] Federazione Italiana Medici di Medicina Generale (FIMMG), Rome, Italy
[vv] Nuclear Medicine Unit, AOU Città della Salute e della Scienza di Torino, Turin, Italy
[ww] Department of Medical Sciences, University of Turin, Turin, Italy
[xx] Division of Gerontology and Geriatrics, Department of Medicine and Surgery, University of Perugia, Perugia, Italy
[yy] Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden
[zz] Division of Geriatric and Intensive Care Medicine, University of Florence & Azienda Ospedaliero-Universitaria Careggi, Florence, Italy
[aaa] Neurology, Neurophysiopathology, and Stroke Unit, Santo Stefano Hospital, Prato, Italy
[bbb] Neurology and Stroke Unit, Luigi Sacco University Hospital, Milan, Italy
[ccc] Department of Biomedical and Clinical Sciences, Neuroscience Research Center, University of Milan, Milan, Italy
[ddd] Department of Neurorehabilitation Sciences, Casa di Cura Igea, Milan, Italy
[eee] Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy
[fff] Neuroradiology Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[ggg] Department of Neuroscience, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Florence, Italy
[hhh] IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy
[iii] Fondazione Villa Serena per la Ricerca, Città Sant'Angelo, Pescara, Italy
[jjj] Associazione Italiana Malattia Alzheimer-AIMA, Milan, Italy
[kkk] Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy
[lll] Neuroradiology Unit, San Salvatore Hospital, L'Aquila, Italy
[mmm] Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy
[nnn] Neurology Unit and Centre for Cognitive Disorders and Dementia, ARNAS Garibaldi, Catania, Italy
[ooo] Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy
[ppp] Neurology Unit, Department of Continuity of Care and Frailty, ASST Spedali Civili di Brescia, Brescia, Italy
[qqq] Neurobiorepository and Advanced Biomarkers Laboratory, University of Brescia & ASST Spedali Civili di Brescia, Brescia, Italy
[rrr] Brain Health Center, University of Brescia, Brescia, Italy

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ABSTRACT

With the European authorisation of lecanemab and donanemab, Italy is entering the era of disease-modifying therapy for early symptomatic Alzheimer's disease. The Italian Expert Panel on Alzheimer (EPA), which convened 21 scientific societies and patient associations and published a first set of intersocietal recommendations in 2025, was reconvened in Rome on 24 January 2026 (EPA2) to address the operational gaps that had emerged during the implementation of that document. A modified Delphi process was adopted to formalise consensus on the most controversial points raised during the meeting. Thirty-six declarative statements covering five domains, namely the tiered organisation of the Centres for Cognitive Disorders and Dementia (CDCD), clinical staging and treatment monitoring, eligibility considerations in mild cognitive impairment and atypical phenotypes, composition of the multidisciplinary team, and magnetic resonance imaging thresholds, ARIA monitoring and biomarker pathway, were submitted to a multidisciplinary panel of experts. Strong agreement was reached on the large majority of statements, providing quantitative endorsement for a competence-based reorganisation of the CDCD network, the harmonised use of the Clinical Dementia Rating, an explicit composition of the multidisciplinary team, trial-aligned magnetic resonance imaging eligibility criteria with a move towards risk-adapted ARIA monitoring, and a stepwise biomarker pathway integrating plasma assays, cerebrospinal fluid analysis on automated platforms and amyloid positron emission tomography. The document provides Italian regional and national health systems, prescribing centres and reimbursing authorities with a quantitative blueprint for the appropriate, equitable and sustainable use of anti-amyloid monoclonal antibodies in clinical practice.

1. Introduction

The authorisation of lecanemab and donanemab in the European Union has marked the transition of early symptomatic Alzheimer's disease (AD) from a clinical syndrome managed mainly with symptomatic agents to a biologically defined condition for which disease-modifying therapy (DMT) is, for the first time, available [1,2]. Treatment requires a biologically confirmed diagnosis of brain amyloidosis, careful clinical and radiological screening for risk factors of amyloid-related imaging abnormalities (ARIA), strutctured infusion logistics,

longitudinal monitoring with magnetic resonance imaging (MRI) and clinical scales, and an explicit framework for treatment discontinuation [3–6]. Across Europe, several national societies have produced appropriate-use recommendations to translate trial-derived eligibility and safety rules into context-specific clinical practice [7–11].

In Italy, the Italian Expert Panel on Alzheimer (EPA), convened by the Italian Society of Neurology (SIN) and including 19 Italian scientific societies, federations and patient associations, published in 2025 a first set of intersocietal recommendations addressing the structural reorganisation of the diagnostic-therapeutic pathway for the implementation and appropriate use of anti-amyloid monoclonal antibodies in AD [10]. That document outlined a patient journey beginning with the early identification of cognitive impairment by general practitioners (GPs), continuing through specialist evaluation at the Centres for Cognitive Disorders and Dementia (Centri per i Disturbi Cognitivi e Demenze, CDCD), and eventually culminating, in carefully selected cases, in DMT initiation. It also proposed a stepwise biomarker strategy and minimum requirements for prescribing and infusion centres. The recommendations were qualitative and necessarily nonspecific on several open issues that required further multidisciplinary consensus.

In the months following publication, several operational and organisational uncertainties emerged through regional implementation processes, real-world experience gained from compassionate-use programs, and an official request from the Italian Medicines Agency (AIFA) to the Italian Society of Neurology (SIN) for further technical clarification. These included the formal tiering of CDCDs by competence and resources rather than by geography; the consistent use of the Clinical Dementia Rating (CDR) for eligibility, monitoring and termination; the composition of the multidisciplinary team responsible for ARIA risk assessment; the harmonisation of MRI thresholds and risk-adapted monitoring; the integration of plasma biomarkers into the diagnostic algorithm without abandoning cerebrospinal fluid (CSF)-based biological confirmation; the role of amyloid positron emission tomography (PET) at baseline and during treatment; and the management of discordant biomarker profiles, atypical phenotypes and *APOE*-related ARIA risk.

Against this background, the EPA was reconvened in Rome on 24 January 2026 (EPA2). The meeting was organised in thematic sessions devoted to the reorganisation of the CDCD network in light of Ministerial Decree 77/2022 and the National Dementia Plan [12,13], clinical staging and frailty assessment, fluid and PET biomarkers, MRI/ARIA monitoring, and *APOE* genetics. Each session combined dedicated presentations by experts of the participating societies with structured plenary discussion. The themes most frequently raised during the discussion, and those for which the existing 2025 recommendations were felt to be insufficiently prescriptive, were converted into 35 declarative statements covering five domains and submitted to a modified Delphi process between February and April 2026.

The aim of the present position paper is to provide a quantitative, intersocietal, and multidisciplinary consensus on the main operational controversies that have emerged following publication of the 2025 Italian intersocietal recommendations. Furthermore, it seeks to translate this consensus into a coherent, evidence-based framework that may serve as a practical reference for Italian CDCDs, prescribing centres, regional and national health authorities, and reimbursement agencies. Finally, the document aims to align the Italian approach with the appropriate-use recommendations recently developed in other European countries, while preserving the specific features of the Italian healthcare system, which is regionally organised and characterised by substantial heterogeneity in the availability of biomarker laboratories, neuroradiological expertise, and nuclear medicine resources. The conceptual framework of the patient journey remains unchanged from the 2025 document; this paper extends and operationalises it by adding a quantitative consensus on more specific elements (network tiering, scales, team composition, MRI thresholds, biomarker platforms and cut-offs, risk-adapted monitoring) that determine whether the framework can actually be implemented in everyday clinical practice. The specific contribution of the present document relative to the 2025 recommendations is summarised in Supplementary Table 1, which indicates, for each domain, whether the recommendation is reaffirmed, modified, entirely new, or driven by evidence that became available after publication of the previous paper.

2. Methods

The Delphi panel consisted of delegates representing 21 Italian scientific societies, federations and patient associations actively engaged in the diagnosis and treatment of cognitive disorders and dementia. The participating organisations were the Academy of Geriatrics (AG); the Italian Association of Neuroradiology (AINR); the Italian Association of Nuclear Medicine and Molecular Imaging (AIMN); the Italian Alzheimer's Disease Patient Association (AIMA); the Italian Association of Psychogeriatrics (AIP); the Italian Federation of General Practitioners (FIMMG); the Network of IRCCS for Neuroscience and Neurorehabilitation (RIN); the Italian Society of Clinical Biochemistry and Clinical Molecular Biology (SIBIoC); the Italian Society of Pharmacology (SIF); the Italian Society of Gerontology and Geriatrics (SIGG); the Italian Society of Hospital and Community Geriatrics (SIGOT); the Italian Society of Human Genetics (SIGU); the Italian Society of General Practitioners and Primary Care (SIMG); the Italian Society of Leadership and Management in Medicine (SIMM); the Italian Society of Neurology (SIN); the Italian Society of Neurology Autonomous Association for Dementias (SINdem); the Italian Society of Neuropsychology (SINP); the Italian Society of Neuroscience (SINS); the Italian Society of Clinical Pathology and Laboratory Medicine (SIPMeL); the Italian Society of Medical and Interventional Radiology (SIRM); and the Italian Society of Hospital Neurology (SNO). Each participating society was asked to identify, within its own membership, the delegate with the greatest expertise in the topics covered by the EPA2 programme, so that the selection of the individual experts rested with the societies themselves. In addition, the organising committee (A.B., A.P.) invited a number of experts of recognised national standing in the field of Alzheimer's disease, selected after careful review of their clinical and scientific activity in the areas covered by the programme and of their contribution to the 2025 Italian intersocietal recommendations, so as to ensure continuity of expertise with the previous document. The writing committee additionally verified that each of the five thematic domains was covered by at least three panellists with specific competence in that domain, so as to combine institutional representation with individual expertise and to limit response bias arising from an unbalanced composition of the panel.

A modified, three-step Delphi process was adopted, in line with the methodology used by other intersocietal recommendations [14,15]. The process was preceded by a preparatory phase in which the organising committee (A.B., A.P.) systematically reviewed the available evidence, the appropriate-use recommendations published in other countries, and the criticisms and requests for clarification that had followed publication of the 2025 Italian recommendations. On this basis, the topics considered to require multidisciplinary discussion were identified and organised into the thematic programme of the meeting. The first step was a deliberative exchange during the EPA2 in-person meeting on 24 January 2026, in which each session ended with a moderated plenary discussion designed to identify the open issues requiring a quantitative consensus. In the second step, a writing committee (A.B., A.P.) drafted the declarative statements, working on the slide sets of all presentations and on the verbatim transcript of the meeting, produced by an external professional transcription service. The third step was anonymous voting on the final set of statements, through a structured online questionnaire (Google Forms) administered between February and April 2026. An issue raised in the plenary discussions was converted into a statement only if it satisfied three criteria: it had been raised by panellists of at least two different disciplines or societies, it concerned an operational decision required in routine clinical practice, and it was not already

unambiguously resolved by the 2025 EPA document. Each draft statement was then independently reviewed for clarity, non-ambiguity and absence of suggestive wording by two further members of the writing committee (M.B., F.A.) who had not participated in the drafting, with discrepancies resolved by discussion until unanimity; in one case the formulation was revised to a more neutral wording before being submitted to the vote. Statements were grouped into five domains: tiering and organisation of the CDCD network; clinical staging and treatment monitoring; eligibility considerations in mild cognitive impairment (MCI), atypical phenotypes and concurrent symptomatic therapies; composition of the multidisciplinary team; and MRI thresholds, ARIA monitoring and biomarker pathway (CSF, plasma, amyloid PET, APOE). For each statement, panellists were asked to express their level of agreement on a four-point Likert scale (totally agree, somewhat agree, somewhat disagree, totally disagree), with an additional option to abstain and the possibility of adding free-text comments, which were provided in both rounds. Members of the writing committee attended the meeting as delegates of their own societies and were therefore also entitled to vote; votes were neither weighted nor analysed separately by role. The responses were also analysed as ordinal scores for the assessment of response dispersion reported in Supplementary Table 2.

Consensus categories were defined a priori in line with the same methodological framework: strong agreement when at least 70% of non-abstaining respondents endorsed the statement (totally + somewhat agree); moderate agreement when endorsement was between 50% and 69%; and no agreement below 50%. Statements with strong agreement were retained verbatim in the final document and translated into the recommendations. Statements that did not reach strong agreement at the first round were submitted to a structured online re-discussion among the panellists, preceded by the return to the whole panel of the anonymised distribution of votes and of the verbatim free-text objections recorded at voting, so that reformulation was driven by the documented reasons for dissent rather than by the writing committee's own reading of the result; the original wording was reviewed in light of the discussion and reformulated; in one case, the original statement was reformulated and split into two distinct statements to better reflect the different aspects that had emerged from the discussion. The reformulated statements were then submitted to a second voting round, with absolute majority (>50% agreement among non-abstaining respondents) considered sufficient to declare consensus. This two-tier rule, applying a strict 70% threshold in the first instance and relaxing it to absolute majority only after structured re-discussion, was not devised *ad hoc* but reproduces a procedure prospectively defined and previously applied in other intersocietal Delphi consensus exercises [14,15]. Statements remaining below the strong-agreement threshold after the second round were not discarded: they are reported in Table 1 with their level of agreement, and the reasons for dissent are discussed alongside the corresponding recommendations. After the voting, the writing committee additionally classified each statement according to the basis of the recommendation, distinguishing statements that reproduce a regulatory requirement, statements derived directly from the pivotal trials, statements supported by indirect or observational evidence, and statements adopted in the absence of direct evidence; this classification is reported in Table 1 and was not submitted to the panel.

3. Results

All invited panellists returned a complete questionnaire in the first round (response rate 100%); strong agreement was reached on 32 of the 35 first-round statements, moderate agreement on two and no agreement on one. The two statements that had reached only moderate agreement were submitted to a structured online re-discussion among the panellists, during which the original wording was reviewed in light of the discussion and reformulated. The reformulated statements were then submitted to a second voting round, which was completed by 88.6% of panellists. The final set of 36 statements endorsed by EPA2 therefore comprises 34 statements with strong agreement, one statement with moderate agreement and one rejected statement. The full list of statements, as endorsed in the final document, with the corresponding consensus levels is reported in Table 1 and visually summarised in Fig. 1. Measures of response dispersion for each statement, comprising the median score, the interquartile range and the number of abstentions, are reported in Supplementary Table 2.

3.1. Tiered organisation of the CDCD network

The 2025 Italian intersocietal recommendations introduced minimum requirements for prescribing and infusion centres but did not propose a formal tiering of the entire CDCD network [10]. EPA2 reached unanimous consensus that the existing CDCDs should be redefined in three nested levels of competence (A, B and C) aligned with capability rather than with administrative geography (Statement 1). The three-level model derives directly from the architecture of the patient journey [10]. Level A corresponds to the standard CDCD that performs the first specialist evaluation, frailty and functional staging, screening for confounding conditions (depression, sleep disorders, polypharmacy and anticholinergic burden, sensory impairment, undertreated systemic disease) and structured triage with formal referral pathways [16–19] (Statement 2). Level B comprises CDCDs equipped to perform the full eligibility for anti-amyloid monoclonal antibodies assessment, including biological confirmation through CSF or amyloid PET, standardised cognitive and functional staging with the CDR (global and sum of boxes), comprehensive neuropsychological evaluation, baseline MRI with sequences specifically tailored to ARIA risk stratification, and structured multidisciplinary discussion of eligibility with informed counselling (Statement 3) [14,20–22]. Level C identifies the centres accredited to administer DMTs, ensure structured ARIA monitoring through MRI, manage adverse events and fulfil pharmacovigilance obligations, in line with the framework adopted in other European countries [7–9] (Statement 4).

The three levels are nested rather than hierarchical: a Level C centre by definition fulfils the requirements of Level B and Level A, while a Level A or B centre is fully integrated into the network through formal referral pathways. The patient maintains a single ordinary reference at the local CDCD (level A or B), while the Level C centre assumes responsibility for the DMT-specific activities (infusion logistics, ARIA monitoring, dose adjustments, treatment discontinuation) without replacing the overall care, in analogy with the model adopted in oncology and rheumatology day-hospital networks (Statement 5). This division of labour preserves the territorial organisation of the Italian National Health Service mandated by Ministerial Decree 77/2022 and by the National Dementia Plan [12,13]. Access to amyloid PET imaging is a defining feature of Level C competence (Statement 6); "access" does not imply physical co-location of the scanner within the prescribing centre, and may be effectively guaranteed by formal collaborations with neighbouring nuclear medicine units, particularly in regions where the territorial distribution of PET centres is heterogeneous [23]. Levels should be assigned by the Regions against shared national criteria rather than self-declared, and accreditation should be periodically reassessed so that the network remains dynamic. Movement between levels should be possible in both directions according to documented competence, staffing and equipment, allowing a centre that acquires the necessary expertise to be upgraded and a centre that no longer meets the requirements to be reclassified. Interoperable informatics platforms are a prerequisite, both to allow the patient record to travel across the levels of the network and to make accreditation auditable. The specific quality indicators on which periodic reassessment should be based were not submitted to the present Delphi exercise and should be defined together with the Regions and the national registry as a priority for the next phase of implementation.

3.2. Clinical staging and treatment monitoring

Clinical staging defines who is eligible for anti-amyloid monoclonal antibodies, when treatment should be discontinued and how the trajectory of the individual patient should be followed during therapy. The 2025 Italian intersocietal recommendations had already established the principle that disease staging should rely on validated cognitive and functional measures aligned with clinical trial criteria. However, they did not clearly define which instruments should serve as the primary reference for treatment eligibility, longitudinal monitoring, and treatment discontinuation, nor how to balance the methodological rigour required within prescribing centres with the more heterogeneous levels of training and expertise available across the broader CDCD network [10]. EPA2 was therefore asked to convert this principle into operational rules, by selecting the reference scale for treatment eligibility and termination, and by defining how cognitive staging should be tiered across Levels A, B and C of the network and integrated with caregiver-reported outcomes and biological markers of target engagement.

The CDR was endorsed as the formal anchor for treatment eligibility in Italy, in line with the regulatory authorisations of lecanemab and donanemab and with international appropriate-use recommendations [3,4,21,24]. The pivotal trials of lecanemab and donanemab enrolled participants with a CDR-global score of 0.5 (MCI due to AD) or 1 (mild AD dementia) [1,2]. Adopting the CDR-global score as the eligibility instrument ensures direct comparability with pivotal trial populations, integrates cognitive and functional information beyond the reach of the Mini Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA), and promotes a consistent semantics across the network [21,24–26] (Statement 7). Coherently, the panel agreed that progression to a CDR-global of 2 (the transition from mild to moderate dementia) should normally trigger treatment discontinuation, in line with the absence of evidence for clinically meaningful efficacy of anti-amyloid monoclonal antibodies in moderate or severe AD (Statement 8).

The Clinical Dementia Rating sum of boxes (CDR-SB), with its 18-point continuous scale, is more sensitive than the CDR-global to subtle longitudinal change and is therefore endorsed as the reference instrument for longitudinal monitoring of progression and treatment response (Statement 9). It was the primary outcome in CLARITY-AD, where lecanemab slowed decline on the CDR-SB by 0.45 points relative to placebo at 18 months (1.21 versus 1.66, a 27% relative reduction) [1]. In TRAILBLAZER-ALZ 2, in which the CDR-SB was a key secondary outcome, donanemab slowed decline on the CDR-SB by 0.70 points relative to placebo at 76 weeks (1.72 versus 2.42, a 29% slowing of clinical progression in the combined population) [2]. These are aggregate, between-group differences observed in selected trial populations and should not be transposed mechanically to the individual patient. Two methodological caveats deserve explicit acknowledgement. First, the smallest score increment of the CDR-SB is 0.5 points, and the absolute 18-month difference between active treatment and placebo lies at, or even below, this minimum detectable change; at 6 or 12 months, the expected between-group difference is therefore smaller than the resolution of the scale itself. Second, individual disease trajectories are heterogeneous, and a slower-than-expected decline observed in a single patient on treatment cannot be unambiguously attributed to disease modification, just as a continuing decline does not necessarily exclude a treatment effect. For the same reason, *post hoc* "responder analyses" based on applying a minimal clinically important difference threshold to individual score changes should be interpreted with caution. Although such analyses may classify participants as "responders" or "non-responders", they do not establish true individual treatment responses in a parallel-arm trial, because the untreated trajectory of each treated participant remains unknown. Moreover, dichotomizing a continuous outcome such as the CDR-SB may preferentially identify borderline cases in whom small score fluctuations move the participant across an arbitrary threshold, rather than a distinct subgroup experiencing a clearly meaningful benefit [27–29]. Cognitive scales should therefore be used to monitor disease progression in the individual patient and to support structured clinical judgement, rather than as standalone proof of individual response or non-response to treatment.

Translating these principles into Italian clinical practice requires a tiered approach mirroring the architecture of the CDCD network. CDR-global and CDR-SB rating should be considered the reference instruments at Level B and Level C centres, where they anchor eligibility, continuation and discontinuation decisions to a trial-aligned benchmark: at Level B, during the formal eligibility assessment that precedes treatment initiation; at Level C, throughout the structured monitoring of patients on anti-amyloid monoclonal antibodies. The interval between clinical reassessments should be 6 months, in line with the schedule adopted in the pivotal trials [1,2,30] (Statement 10). In Level A centres, the initial identification and triage of potentially eligible patients should primarily rely on a clinical diagnosis of MCI or mild dementia, supported by the lower MMSE threshold already specified in these recommendations [10]. Cognitive screening instruments, including the MoCA, may be used as supportive tools, and published MoCA-to-CDR-SB conversion tables, recently developed on a large multicentric cohort [31], may provide additional support when dedicated CDR expertise is not available. Patients considered potentially eligible should then be referred to a Level B centre for formal eligibility assessment. In CDCDs where neuropsychological expertise is available, a comprehensive multi-domain cognitive assessment calibrated to the patient's pre-morbid cognitive functioning is recommended. During treatment monitoring, the CDR-anchored staging should not be read in isolation. Structured caregiver interviews, neuropsychiatric inventories, concomitant medication review, generic health-related quality of life measures, such as the EQ-5D-5 L, disease-specific patient-reported outcomes, such as the Alzheimer's Disease Quality of Life questionnaire, and caregiver-burden measures, such as the NPI-Q distress score, complete the clinical assessment, while amyloid PET provides a direct marker of target engagement and plasma p-tau217, together with emerging fluid biomarkers, provides a complementary read-out of downstream biological response and treatment-related disease modification. Longitudinal monitoring is therefore best conceived as an integrated clinical and biological dashboard, in which trial-aligned scales, person-centred outcomes and biological target engagement are weighed together to support a structured re-evaluation of the benefit-risk balance whenever the goals of treatment are no longer being met [32]. Operationalising this dashboard at scale will require the definition of a shared minimum dataset that can travel with the patient across the network and feed a national registry capable of generating the Italian real-world evidence on which the next iteration of these recommendations will be built.

3.3. Composition of the multidisciplinary team

The eligibility, treatment and monitoring of a patient on anti-amyloid monoclonal antibodies requires a multidisciplinary team that integrates clinical, cognitive, radiological and laboratory expertise. EPA2 distinguished between necessary and desirable professional figures. "Necessary" identifies the professionals whose contribution is required for every patient undergoing evaluation for anti-amyloid monoclonal antibodies, and who must therefore be structurally part of the team of any centre delivering these treatments. "Desirable" identifies the professionals whose involvement is determined by the clinical characteristics of the individual patient, and who may participate on a referral or consultation basis; when the corresponding clinical condition is present, their contribution becomes necessary for that patient. The distinction therefore reflects the clinical needs of the individual patient and not a hierarchy of importance among the professionals involved. The neurologist is necessary because of the integrated clinical assessment (phenotype, staging, neuropsychiatric and behavioural symptoms, comorbidities, concomitant medication review) that contextualises the radiological findings and guides the eligibility decision, and because of

the responsibility for the interpretation of clinical events that emerge during treatment (Statement 11). The neuroradiologist is essential for the structured reporting of baseline MRI, including quantification of microhaemorrhages on T2*/GRE and SWI sequences, evaluation of superficial siderosis, white matter hyperintensities, application of the criteria for cerebral amyloid angiopathy, and for the longitudinal interpretation of follow-up MRI and the early recognition of ARIA-E and ARIA-H [20,33,34] (Statement 12). In centres where in-house neuroradiology expertise is limited, telereporting and dedicated regional consultation hubs should be activated.

The neuropsychologist is necessary because the standardised cognitive staging required for eligibility (CDR, comprehensive neuropsychological battery) is most reliably performed by a trained neuropsychologist, particularly in atypical phenotypes where MMSE or MoCA alone are insufficient, and because the longitudinal monitoring of treatment response benefits from a multidomain assessment that captures changes in memory, language, visuospatial and executive function, and that is calibrated to the patient's pre-morbid functioning (Statement 13). The specialised nurse acting as case manager represents the operational backbone of the treatment pathway. This role includes coordination of appointments, infusions, MRI and biomarker tests, educating the patient and the caregiver about the treatment, recognising infusion-related reactions, ensuring documentation completeness for the monitoring registry, and acting as the first point of contact for symptomatic concerns between visits. The role aligns with the navigator/coordinator function explicitly recommended in the UK framework [9] and mirrors the model of the dedicated case-manager nurse that several Italian multiple sclerosis centres have successfully embedded in their multidisciplinary teams (Statement 14).

The contribution of the geriatrician begins early in the patient journey and is not confined to the assessment of safety risk. Frailty assessment is one of the first determinants of appropriate treatment allocation, and its greatest value lies in older adults with multimorbidity, polypharmacy or mild-to-moderate frailty, in whom the evaluation of biological reserve, functional trajectory, competing risks and patient-centred goals may substantially influence shared decision-making. The involvement of a geriatrician is desirable in older patients or, independently of age, in the presence of multimorbidity, polypharmacy, or frailty of any grade, when clinical decision-making extends beyond a purely neurological perspective. Frailty should be ascertained with validated instruments and graded as mild, moderate or severe, rather than being considered only when clinically evident. In this context, the geriatrician contributes to the multidimensional assessment of frailty, biological reserve and life expectancy, while evaluating the impact of multimorbidity, polypharmacy and cardiovascular comorbidities on clinical trajectory, treatment tolerability and overall care planning. This approach also supports optimization of potentially inappropriate medications preventing drug interactions, management of antithrombotic therapies and development of individualized follow-up strategies tailored to the patient's global condition [17,18,35–37] (Statement 15). The nuclear medicine physician is a necessary component of the multidisciplinary team for treatment eligibility assessment, particularly for the interpretation of amyloid PET (atypical distribution patterns, correlation between centiloid burden and clinical severity, discordance between visual reading and semi-quantitative analysis), as well as for monitoring and treatment-discontinuation decisions whenever amyloid PET is part of the diagnostic or follow-up workflow [23,38–41] (Statements 16 and 17).

3.4. Eligibility in mild cognitive impairment, atypical phenotypes and concomitant therapies

Throughout this document, eligibility is understood as an appropriateness and benefit-risk judgement, not as a prioritisation strategy driven by limited treatment availability. The purpose of the criteria set out below is to identify the patients in whom the biological, clinical and functional profile supports a meaningful expected benefit at an acceptable level of risk, and equally to identify those in whom it does not. The proposal that MCI candidates should show documented clinical progression during the six months preceding treatment was the most divisive of the entire Delphi process; the original statement did not reach strong agreement, and the reformulated version, which explicitly recognised that clinical progression could be documented by a formal clinical evaluation and/or by clinical history from the patient and/or the caregiver, reached only moderate agreement in the second voting round (63% of non-abstaining respondents) (Statement 18). The split reflects two legitimate but conflicting interpretations of the trial evidence. On one hand, focusing treatment on documented fast progressors limits the exposure to potential harm of patients who are clinically stable and in whom the expected benefit is correspondingly less certain; on the other, restricting eligibility to those with documented decline may delay treatment in the very patients best positioned to benefit, since pivotal trial subgroup analyses suggest larger absolute benefits in less advanced disease [1,2,42]. The panel's overall position is that progression should be considered when the diagnostic picture is uncertain, when there is suspicion of confounding conditions, or when a re-evaluation is needed before committing to treatment, but that mandatory six-month progression is not, on current evidence, an appropriate routine eligibility criterion. Coherently, eligible MCI patients should begin treatment as soon as possible (Statement 19). At the same time, the diagnostic process required to confirm eligibility (clinical evaluation, neuropsychological assessment, MRI, biomarker confirmation, informed consent and *APOE* counselling, multidisciplinary discussion) has its own intrinsic timeline and should not be compressed beyond what is needed to deliver a high-quality, safe eligibility decision.

The use of acetylcholinesterase inhibitors or memantine, and the timing at which symptomatic therapy is started, should not affect eligibility for, or delay initiation of, anti-amyloid monoclonal antibodies (Statement 20). Pivotal trials of lecanemab and donanemab allowed concomitant symptomatic therapy and used it as a stratification factor; *post hoc* analyses found no significant interaction between symptomatic agents and the magnitude of the DMT effect [1,2]. International appropriate-use frameworks converge on this position [7–9].

Atypical AD phenotypes, including the logopenic variant of primary progressive aphasia (lvPPA), posterior cortical atrophy (PCA), the behavioural/dysexecutive variant of AD and frontal presentations, are heterogeneous in clinical course and biological substrate and were not formally enrolled in the pivotal phase 3 trials [43–46]. The panel adopted a pragmatic position: patients with atypical phenotypes should be treated when the underlying amyloid pathology is plausibly explaining the clinical syndrome, with three convergent elements required: a clinical syndrome consistent with an atypical AD phenotype validated by formal neuropsychological assessment and structured imaging review, biological confirmation of brain amyloidosis with concordant tau biomarkers (A+T+), and the explicit judgement of a multidisciplinary team that AD pathology is the most likely cause. The decision is to be made case by case, with a high threshold for treatment when the connection between the amyloid pathology and the clinical syndrome is uncertain (Statement 21).

3.5. MRI thresholds and risk-adapted ARIA monitoring

Magnetic resonance imaging is the cornerstone of safety in the era of anti-amyloid monoclonal antibodies. The 2025 Italian intersocietal recommendations had already endorsed a structured baseline and follow-up MRI protocol, anchored to the international standards and explicitly intended to detect amyloid-related imaging abnormalities (ARIA), to characterise the underlying cerebrovascular substrate and to inform the eligibility decision [6,10,33]. They did not, however, take an explicit position on the microhaemorrhage threshold to be applied in clinical practice, on the relative role of T2*/gradient-echo (GRE) and susceptibility-weighted imaging (SWI) sequences, or on the evolution of

monitoring schedules from the current uniform protocols towards a risk-adapted strategy. EPA2 was therefore asked to operationalise these aspects in three converging directions: by aligning the Italian framework with the European Medicines Agency (EMA) labels of lecanemab and donanemab on the maximum microhaemorrhage burden compatible with treatment; by clarifying how to use GRE and SWI sequences both at baseline and during longitudinal monitoring; and by setting out the conceptual basis for moving, over the coming years, from a "one-size--fits-all" MRI schedule to risk-stratified monitoring driven by drug, host and biomarker characteristics.

The microhaemorrhage threshold used to define MRI eligibility is one of the most clinically and operationally important rules in the safe use of anti-amyloid monoclonal antibodies, since it determines both individual eligibility and the size of the treatable population. EPA2 strongly endorsed the threshold of more than four microhaemorrhages on baseline T2*/GRE imaging adopted in the pivotal trials of lecanemab and donanemab for treatment exclusion and incorporated into the European Medicines Agency (EMA) risk-minimisation measures [1,2,47–49]. The Italian framework therefore aligns directly with the EMA Summary of Product Characteristics for lecanemab and donanemab, which contraindicates treatment initiation in patients with more than four microhaemorrhages, with superficial siderosis, with prior intracerebral haemorrhage, with vasogenic oedema or with other findings suggestive of cerebral amyloid angiopathy at baseline MRI. The more restrictive proposal of a >1-microhaemorrhage threshold was explicitly rejected by the panel (Statements 22 and 23). It should however be acknowledged that a higher baseline burden of cerebral microhaemorrhages, even within the eligibility range, has been consistently associated with an increased risk of treatment-emergent ARIA, both ARIA-E and ARIA-H, in pivotal trials and in real-world cohorts [50–55]; the >4-microhaemorrhage cut-off should therefore be regarded as a minimum safety threshold for eligibility, not as a reassurance that ARIA risk is uniform across patients who meet it, and the absolute number and distribution of microhaemorrhages should be weighed by the multidisciplinary team together with the other established ARIA risk modifiers (drug, *APOE* ε4 status, baseline amyloid burden and prior ARIA history).

Both gradient-echo (GRE) and susceptibility-weighted imaging (SWI) sequences should be acquired at baseline and at every follow-up MRI examination. GRE remains the reference sequence for the application of the >4-microhaemorrhage rule, since it is the modality on which the pivotal trial eligibility was defined; SWI is more sensitive than GRE for the detection of small microhaemorrhages, and the additional information it provides should be used as a stratification tool when GRE eligibility criteria are met but a substantial additional burden is detected on SWI [56,57]. In particular, head-to-head data from the TRAILBLAZER-ALZ 6 trial have shown that, in donanemab-treated participants who were eligible on GRE-based criteria, the presence of more than four microhaemorrhages on baseline SWI was independently associated with a more than twofold increase in the risk of treatment-emergent ARIA-E by 76 weeks (odds ratio 2.3, $p = 0.039$), an association that was not detected when the same threshold was applied to GRE alone [58]. The SWI count therefore should not be used to override the trial-aligned GRE-based eligibility threshold but provides an additional layer of pre-treatment risk stratification that should be explicitly considered by the multidisciplinary team (Statement 24). The same logic applies during longitudinal monitoring: SWI should be acquired at every follow-up examination, since a disproportionate emergence of new microhaemorrhages or of cortical superficial siderosis on SWI that is not appreciable on GRE, while not strictly modifying treatment decisions anchored on GRE-defined criteria, may inform a more conservative interpretation of the overall safety profile and prompt reassessment of the dosing regimen, of the monitoring intensity or of the continuation of treatment within the multidisciplinary team. Moreover, the same scanner and the same field strength should be used at baseline and at follow-up to ensure comparability of microhaemorrhage counts. Beyond eligibility, EPA2 strongly endorsed the principle that MRI surveillance during treatment should evolve from current uniform schedules towards risk-stratified monitoring, integrating four key modifiers: drug-specific risk profiles; *APOE* ε4 genotype, which substantially modulates the absolute risk; baseline amyloid burden expressed in centiloids and possibly the regional distribution (with occipital predominance emerging as a candidate risk modifier) [50,52,59,60]; and personal history of ARIA, particularly recurrent events. Although each of these factors has been individually shown to modulate ARIA risk, integrated risk-prediction models that combine them are not yet available; the development and prospective validation of composite ARIA risk scores, ideally incorporating the additional information provided by SWI, should be regarded as a research priority and could in the near future support truly individualised, risk-tailored MRI monitoring schedules. Implementation must be supported by prospective registries and must avoid premature divergence from the EMA-mandated minimum schedules (Statement 25).

3.6. Fluid biomarkers

The biological confirmation of brain amyloidosis is the gateway to anti-Aβ mAb treatment, and the Italian network must therefore rely on a fluid biomarker pipeline that is both analytically robust and operationally sustainable. The 2025 Italian intersocietal recommendations had already endorsed the principle of biomarker-confirmed diagnosis and outlined a stepwise pathway in which CSF analysis on fully automated, CE-IVDR-certified platforms for Aβ42/Aβ40 and phosphorylated tau was the cornerstone of biological confirmation, with amyloid positron emission tomography (PET) reserved for selected scenarios [10]. Beyond this established CSF framework, EPA2 was prompted to revisit the biomarker section by the rapid clinical maturation of plasma p-tau217: pivotal studies have shown high accuracy for the detection of AD pathology against both amyloid PET and CSF reference standards [61–66], and in May 2026 two plasma p-tau217 assays, applied to fully automated platforms, obtained CE-IVDR certification in Europe (Lumipulse G pTau 217 Plasma, Fujirebio; Elecsys plasma pTau 217, Roche).

This advance makes it possible to develop a more efficient and scalable triage strategy across both primary and specialist care settings, substantially improving early identification and prioritisation of patients with a high probability of underlying Alzheimer's disease pathology. Within this framework, plasma biomarkers may progressively assume an increasingly relevant role not only in triaging, but also in the biological characterisation of patients, particularly when supported by validated analytical platforms and appropriate quality-control standards. Nevertheless, at the present stage of evidence, formal eligibility for anti-amyloid monoclonal antibody treatment should still be confirmed either through CE-IVDR-approved CSF biomarkers or by amyloid PET imaging.

EPA2 agreed on a two-tier role for plasma biomarkers in the current Italian context, in which the diagnostic and the treatment-eligibility steps are treated as conceptually distinct. For the diagnostic evaluation of a patient with suspected AD, plasma p-tau217 (or the p-tau217/Aβ42 ratio) is used in a two-cut-off scheme that stratifies patients into a low, an intermediate and a high probability of AD pathology, with the intermediate group referred for further confirmation by CSF analysis or amyloid PET [64,67]; when these cut-offs are calibrated for a positive predictive value above 95%, the great majority of patients fall into the low- or high-probability category and can be classified on plasma alone, so that the proportion requiring confirmatory CSF or PET decreases substantially without any loss of diagnostic accuracy (Statement 26). Operationally, this means that, when integrated with the clinical picture, a clearly positive plasma p-tau217 result can on its own be considered sufficient to support a biological diagnosis of AD, and a clearly negative result effectively rules it out, while only the intermediate group needs to proceed to second-line biomarker assessment. For the eligibility decision to anti-amyloid monoclonal antibodies, conversely, plasma biomarkers should not yet be used as the sole

confirmation of brain amyloidosis: at the present time, biological eligibility must be established by CSF analysis on a CE-IVDR-approved automated platform or by amyloid PET. Plasma biomarker results must in all cases be interpreted in the clinical context, with awareness of confounders such as chronic kidney disease and high body mass index [68,69]. This conservative position will need to be reassessed periodically as larger real-world and head-to-head data on plasma p-tau217 versus CSF and amyloid PET in eligibility-relevant populations accumulate.

Biological confirmation of AD by CSF analysis should be performed only on fully automated, CE-IVDR-approved platforms, namely Lumipulse (Fujirebio), Elecsys (Roche) or Euroimmun, which have demonstrated robust analytical performance, low inter-laboratory and inter-operator variability, and high concordance with neuropathology [70,71] (Statement 27). Semi-manual ELISA assays should be progressively retired from the eligibility pathway, internal and external quality control programmes should be a prerequisite, and pre-analytical procedures should be standardised across centres in line with international consensus [72]. Shared cut-offs across Italian laboratories are feasible and desirable for each of the validated platforms, with the Aβ42/Aβ40 ratio generally preferred over Aβ42 alone because it is less affected by inter-individual differences in amyloid metabolism and shows higher concordance with amyloid PET and neuropathology [73,74]. The goal is not to impose a single nationwide cut-off across platforms, which would be analytically inappropriate, but to ensure that each platform has a validated and clinically actionable threshold that can be shared across users of that platform (Statement 28). In the presence of a discordant CSF profile (A+/T- or A-/T+), amyloid PET should be performed to definitively confirm or rule out brain amyloidosis, in line with the other European recommendations and the appropriate-use criteria for amyloid PET [23,75] (Statement 29).

3.7. Amyloid PET and centiloid quantification

Amyloid PET correlates strongly with neuropathological amyloid plaque burden [76–78]. In the Italian context, the panel agreed on a hierarchical pathway in which CSF analysis is the first-line biological confirmation, and amyloid PET is reserved for patients with indeterminate or contradictory CSF biomarkers, for those with a contraindication to lumbar puncture, and for those who refuse the procedure (Statement 30). This use is consistent with the role of amyloid PET in the European intersocietal recommendations for the biomarker-based diagnosis of neurocognitive disorders [14] and with the appropriate-use criteria [23,75]. While amyloid PET is not the first-line diagnostic tool in Italy, EPA2 considered that a baseline amyloid PET would be desirable in all patients eligible for anti-amyloid monoclonal antibodies when feasible, and is most informative in patients who will be treated with donanemab and in those at higher ARIA risk. In fact, a baseline scan, semi-quantified in centiloids, provides three complementary pieces of information not currently available from CSF: the absolute amyloid burden (with prognostic value for ARIA risk), the regional distribution (potentially relevant for ARIA-E risk), and the baseline against which post-treatment scans can be compared (Statement 31). Furthermore, emerging evidence suggests that Centiloid-based amyloid burden can provide staging information by predicting the onset of concomitant tauopathy and tau-PET positivity [79]. Once fully operationalized, this approach could help identify the best candidates for targeted therapies, serving as a surrogate for the prognostic value of tau-PET (which is presently not available in Europe.

TRAILBLAZER-ALZ 2 introduced a treatment-to-target paradigm in which donanemab is continued until amyloid clearance is documented on PET (centiloid value below a defined threshold), at which point treatment is discontinued [2]. EPA2 strongly endorsed the principle that an amyloid PET should be performed after donanemab initiation to document amyloid clearance and to inform the decision to discontinue treatment (Statement 32). The optimal timing of the first post-treatment scan is not yet established and is likely to depend on the baseline amyloid burden expressed in centiloids: for example, an earlier scan (at around 6 months) may be reasonable in patients with a low baseline burden, in whom clearance is more likely to be reached sooner, while a later scan (at around 12 months) may be more informative in those with a higher baseline burden, in whom clearance typically takes longer [80]. A negative amyloid PET at 6 or 12 months should prompt treatment discontinuation, thereby reducing patient and caregiver burden, drug costs and pressure on health services (Statement 33). The precise centiloid thresholds for post-treatment negativity should be harmonised with the international consensus on the Treatment-Amyloid-Clearance (TRAC) framework and updated periodically [39]. The change in plasma p-tau217 (and to a lesser extent p-tau181) from baseline correlates with amyloid reduction at PET and may eventually serve as a gate to define the timing for PET monitoring [80], although this approach is not yet ready for routine clinical implementation (Statement 34). In keeping with the indications emerging from previous statements, the panel agrees that both at baseline and during monitoring, amyloid PET reports should always include semi-quantitative centiloid analysis, complemented by qualitative interpretation by a nuclear medicine physician of regional uptake patterns and of any discordance between the visual reading and the centiloid value (Statement 35).

3.8. APOE genotyping

APOE genotyping is a fundamental element of the eligibility and risk-stratification process for anti-amyloid monoclonal antibodies, with *APOE* ε4 status, and particularly homozygosity, the strongest known modifier of ARIA risk [1,2,81]. The current EMA authorisation of lecanemab and donanemab restricts treatment to *APOE* ε4 heterozygotes and non-carriers, while ARIA risk in heterozygotes remains higher than in non-carriers and warrants intensified counselling and monitoring. Recent technological developments have introduced complementary approaches based on the quantification of the *APOE* protein and its isoforms, but these methods are not yet sufficiently validated to substitute for genotyping in the eligibility decision [82,83]. The eligibility decision must therefore continue to rely on the established methodology (DNA-based genotyping), with formal pre-test counselling, structured documentation of the result and integration of the genotype into the multidisciplinary discussion on eligibility and ARIA risk-stratification (Statement 36).

4. Discussion

The implementation of anti-amyloid monoclonal antibodies in early symptomatic Alzheimer's disease represents a decisive shift for the Italian dementia-care system. It does not simply introduce new drugs into an existing pathway, but requires the construction of an integrated, biologically anchored, safety-oriented and continuously monitored model of care. The EPA2 consensus extends the qualitative framework of the 2025 Italian intersocietal recommendations into a quantitative, multidisciplinary action plan for the appropriate use of anti-amyloid monoclonal antibodies in Alzheimer's disease in Italy. By bringing together 21 scientific societies, professional federations and patient representatives, and by translating multidisciplinary discussion into a structured Delphi process, this position paper defines the organisational, clinical, biomarker and imaging conditions under which disease-modifying therapy can be introduced in Italy in a clinically responsible and equitable manner. Of the 36 statements, 20 address questions on which the 2025 document took no position, 11 modify or operationalise an existing recommendation, 4 reaffirm one while formally submitting the alternative to a vote, and 1 responds directly to evidence that became available after publication of the previous paper. The basis of each recommendation is reported in Table 1. Only two of the 36 statements simply reproduce a regulatory requirement, whereas 19 rest predominantly on expert opinion in areas where direct evidence is

Table 1
Delphi statements and corresponding levels of agreement.

Statement	Agreement level	Basis of recommendation
1. CDCDs should be defined in levels of competences (A, B and C).	Strong agreement (100%)	Expert opinion
2. A CDCD should be considered competent at level A if it is able to ensure timely patient access, perform a standardized clinical and functional baseline assessment, appropriately screen for confounding conditions, and activate a structured triage and follow-up pathway with the local network.	Strong agreement (100%)	Expert opinion
3. A CDCD should be considered competent at level B if it can independently complete the full eligibility assessment for disease modifying therapies, including biological confirmation of Alzheimer's disease, standardized cognitive and functional staging, comprehensive neuropsychological evaluation, baseline MRI assessment with ARIA-relevant sequences and risk stratification, structured multidisciplinary discussion of eligibility, and informed counselling regarding the benefits, risks and uncertainties of treatment.	Strong agreement (97%)	Expert opinion
4. A CDCD should be considered competent at level C if it is able to safely administer disease modifying therapies, ensure structured MRI and ARIA monitoring, manage treatment related adverse events, and fulfil all pharmacovigilance and regulatory requirements.	Strong agreement (100%)	Expert opinion
5. The patient maintains a single ordinary reference at the local CDCD (level A/B), while level C assumes responsibility for the disease modifying therapy without replacing the overall care.	Strong agreement (94%)	Expert opinion
6. A CDCD competent at level C should have access to amyloid PET imaging.	Strong agreement (92%)	Expert opinion
7. The CDR-global score should be used to define eligibility to treatment.	Strong agreement (91%)	Trial evidence; regulatory
8. The CDR-global score should be used to define treatment termination (i.e., when a CDR-global score of 2 is reached).	Strong agreement (85%)	Expert opinion
9. The CDR-sum of boxes should be used to monitor progression and treatment response.	Strong agreement (91%)	Trial evidence
10. A patient on anti-amyloid treatments should be assessed every 6 months to determine disease progression.	Strong agreement (92%)	Trial evidence
11. A neurologist is a necessary professional figure in the multidisciplinary team for ARIA risk assessment.	Strong agreement (97%)	Expert opinion
12. A neuroradiologist is a necessary professional figure in the multidisciplinary team for ARIA risk assessment.	Strong agreement (100%)	Expert opinion
13. A neuropsychologist is a necessary professional figure in the multidisciplinary team for treatment management.	Strong agreement (95%)	Expert opinion
14. A specialised nurse with case manager role is a necessary professional figure in the multidisciplinary team for treatment management.	Strong agreement (90%)	Expert opinion
15. A geriatrician is a desirable professional figure in the multidisciplinary team for ARIA risk assessment in older patients with moderate-to-severe frailty.	Strong agreement (92%)	Expert opinion
16. A nuclear medicine physician is a necessary professional figure in the multidisciplinary team for treatment eligibility assessment, particularly for the interpretation of amyloid PET (e.g., atypical distribution patterns, correlation between centiloid burden and clinical severity, discrepant results between visual read and centiloids).	Strong agreement (81%)	Expert opinion
17. A nuclear medicine physician is a desirable professional figure in the multidisciplinary team for treatment eligibility assessment, particularly for the interpretation of amyloid PET (e.g., atypical distribution patterns, correlation between centiloid burden and clinical severity, discrepant results between visual read and centiloids).	Strong agreement (92%)	Expert opinion
18. Patients in the prodromal phase of Alzheimer's disease (mild cognitive impairment) who are eligible for anti-amyloid therapies should show evidence of clinical progression during the six months preceding treatment initiation, as documented by formal clinical evaluation and/or clinical history from the patient and/or caregiver.	Moderate agreement (63%)	Expert opinion
19. Patients in the prodromal phase of Alzheimer's disease (mild cognitive impairment) who are eligible for treatment with anti-amyloid therapies should begin treatment as soon as possible.	Strong agreement (95%)	Indirect evidence
20. Neither the use of AChEIs or memantine, nor the timing of starting symptomatic therapy, should influence whether a patient is eligible for, or delay initiation of anti-amyloid treatments.	Strong agreement (95%)	Trial evidence
21. Patients with atypical phenotypes should be treated when the underlying pathology (i.e., amyloidosis) is plausibly explaining the clinical syndrome.	Strong agreement (92%)	Expert opinion
22. The treatment exclusion threshold should be set at more than 4 microhaemorrhages on baseline MRI with GRE sequences.	Strong agreement (97%)	Regulatory
23. The treatment exclusion threshold should be set at more than 1 microhaemorrhages on baseline MRI with GRE sequences.	No agreement (34%)	Regulatory
24. MRI should be performed with GRE and SWI sequences; the latter may help to stratify the risk of ARIA when GRE criteria are met but other microhaemorrhages are identified on SWI.	Strong agreement (97%)	Trial evidence
25. Refined and risk-adapted ARIA monitoring strategies should be implemented to move from "one-size-fits-all" MRI schedules to risk-stratified monitoring, integrating drug-specific risk profiles (donanemab vs lecanemab), genetic risk (APOE ε4), baseline amyloid burden and ARIA history.	Strong agreement (97%)	Indirect evidence

(*continued on next page*)

Table 1 (*continued*)

Statement	Agreement level	Basis of recommendation
26. Plasma biomarkers, when available, should be used to triage patients for further CSF analysis.	Strong agreement (92%)	Indirect evidence
27. A biological diagnosis should be confirmed by cerebrospinal fluid analysis only on automated and CE-approved platforms (i.e., Lumipulse, Elecsys, Euroimmun).	Strong agreement (100%)	Indirect evidence; regulatory
28. It is possible to define shared cut-offs for cerebrospinal fluid analysis to define eligibility to anti-amyloid treatments.	Strong agreement (94%)	Indirect evidence
29. Patients with discordant cerebrospinal fluid biomarkers (i.e., A+/T- or A-/T+) should undergo amyloid-PET imaging.	Strong agreement (100%)	Expert opinion
30. An amyloid PET should be performed to support a biological diagnosis of Alzheimer's disease only in patients with indeterminate/contradictory CSF biomarkers, who have a contraindication to lumbar puncture or who refuse to undergo a lumbar puncture.	Strong agreement (92%)	Expert opinion
31. An amyloid PET should be performed in all patients eligible for anti-amyloid treatments because it can provide relevant information for treatment initiation and monitoring (i.e., stratify ARIA risk based on amyloid load and amyloid localization; confirm baseline amyloid burden for subsequent monitoring of clearance).	Strong agreement (84%)	Indirect evidence
32. An amyloid PET should be performed after treatment initiation with donanemab to highlight amyloid clearance and to stop treatment. The timeframe at which amyloid PET is performed is unclear at the present time but could depend on baseline amyloid load.	Strong agreement (95%)	Trial evidence
33. A negative amyloid PET at 6 or 12 months after treatment initiation should prompt treatment discontinuation, thereby reducing patient and caregiver burden, drug costs and pressure on health services.	Strong agreement (95%)	Trial evidence; expert opinion
34. The change in plasma pTau181 and p-Tau217 from baseline correlates with amyloid reduction at amyloid PET and could be used as gate to undergo amyloid PET before treatment completion (i.e., at 6 or 12 months).	Strong agreement (88%)	Indirect evidence
35. Amyloid PET should include semi-quantitative analysis of amyloid burden (i.e., centiloids).	Strong agreement (97%)	Expert opinion
36. At the present time, complementary approaches to APOE genotyping, such as APOE protein quantification, are not sufficiently accurate to determine eligibility for anti-amyloid treatments.	Strong agreement (96%)	Regulatory; expert opinion

Basis of recommendation: "Regulatory" indicates a statement reproducing a requirement of the European Medicines Agency Summary of Product Characteristics or risk-minimisation measures; "Trial evidence" a statement derived directly from the pivotal trials; "Indirect evidence" a statement supported by observational, diagnostic-accuracy or analytical studies; and "Expert opinion" a statement adopted in the absence of direct evidence. This classification was made by the writing committee after the voting and does not constitute a formal grading of the certainty of evidence.

limited or absent, 6 on indirect or observational evidence and 5 on direct evidence from the pivotal trials, the remaining 4 combining a regulatory or trial-derived basis with expert judgement.

Several principles emerge from the consensus. First, access to treatment should be organised through a tiered CDCD network based on competences rather than administrative geography. Level A centres remain essential for early identification, clinical triage and territorial continuity of care; Level B centres perform the full eligibility assessment; Level C centres administer treatment, manage ARIA monitoring and pharmacovigilance, and coordinate discontinuation decisions. This nested model avoids both overcentralisation and fragmentation, preserving the territorial mission of Italian dementia services while concentrating high-complexity procedures where the required expertise is available, thereby avoiding the *de facto* centralisation of dementia care that would be clinically and structurally undesirable.

Second, treatment eligibility and monitoring must be anchored to instruments that are aligned with the pivotal trials but interpreted within clinical judgement. The CDR-global score defines the eligible clinical stage, whereas the CDR-SB provides the reference measure for longitudinal trajectory monitoring. However, clinical scales should not be used as mechanical proof of individual response or non-response. The expected treatment effects are modest at the group level, individual trajectories are heterogeneous, and treatment decisions must integrate cognitive and functional change with patient- and caregiver-reported outcomes, adverse events and biological evidence of target engagement.

Third, safety requires explicit multidisciplinary responsibility. The neurologist, neuroradiologist, neuropsychologist, specialised nurse, nuclear medicine physician and, when appropriate, the geriatrician contribute complementary expertise to the eligibility and monitoring process. MRI criteria must remain aligned with EMA risk-minimisation measures, while SWI should be systematically acquired to refine risk stratification. The consensus also recognises that future monitoring should evolve toward risk-adapted schedules integrating drug, *APOE* genotype, baseline amyloid burden, and cerebrovascular burden, but only after prospective validation.

Fourth, the biomarker pathway must combine innovation with analytical rigour. Plasma p-tau217 is now sufficiently mature to support a probability-based diagnostic triage, reducing unnecessary CSF and PET testing when results are clearly negative or clearly positive. Nevertheless, plasma biomarkers should not yet serve as the sole confirmation of eligibility for anti-Aβ treatment. For this purpose, CSF assessment on fully automated CE-IVDR platforms or amyloid PET remains required. Amyloid PET, particularly when quantified in centiloids, adds information on amyloid burden, regional distribution and treatment-induced clearance, and is especially relevant for donanemab within a treatment-to-target paradigm, including the possibility of treatment discontinuation.

Finally, *APOE* genotyping must be regarded as an integral part of the eligibility pathway. Its role is not merely classificatory, but central to counselling, shared decision-making and ARIA risk stratification.

Some limitations should be acknowledged. Many panellists had contributed to the 2025 EPA recommendations and are actively engaged in the Italian implementation of anti-amyloid therapy. This continuity ensured direct familiarity with the operational problems the present document addresses, but produced a relatively homogeneous panel. The high proportion of statements reaching strong agreement should therefore be read as convergence within an experienced and partly pre-aligned expert community rather than as independent replication by an unselected sample of clinicians, with a corresponding risk of confirming existing practice. Where the panel genuinely diverged, the disagreement is reported transparently and identifies the areas in which independent evidence is most needed.

The procedure adopted also departs from classical Delphi methodology in three respects that should be stated explicitly. First, the statements were formulated after an in-person meeting rather than through an initial round of independent and anonymous idea generation, so that

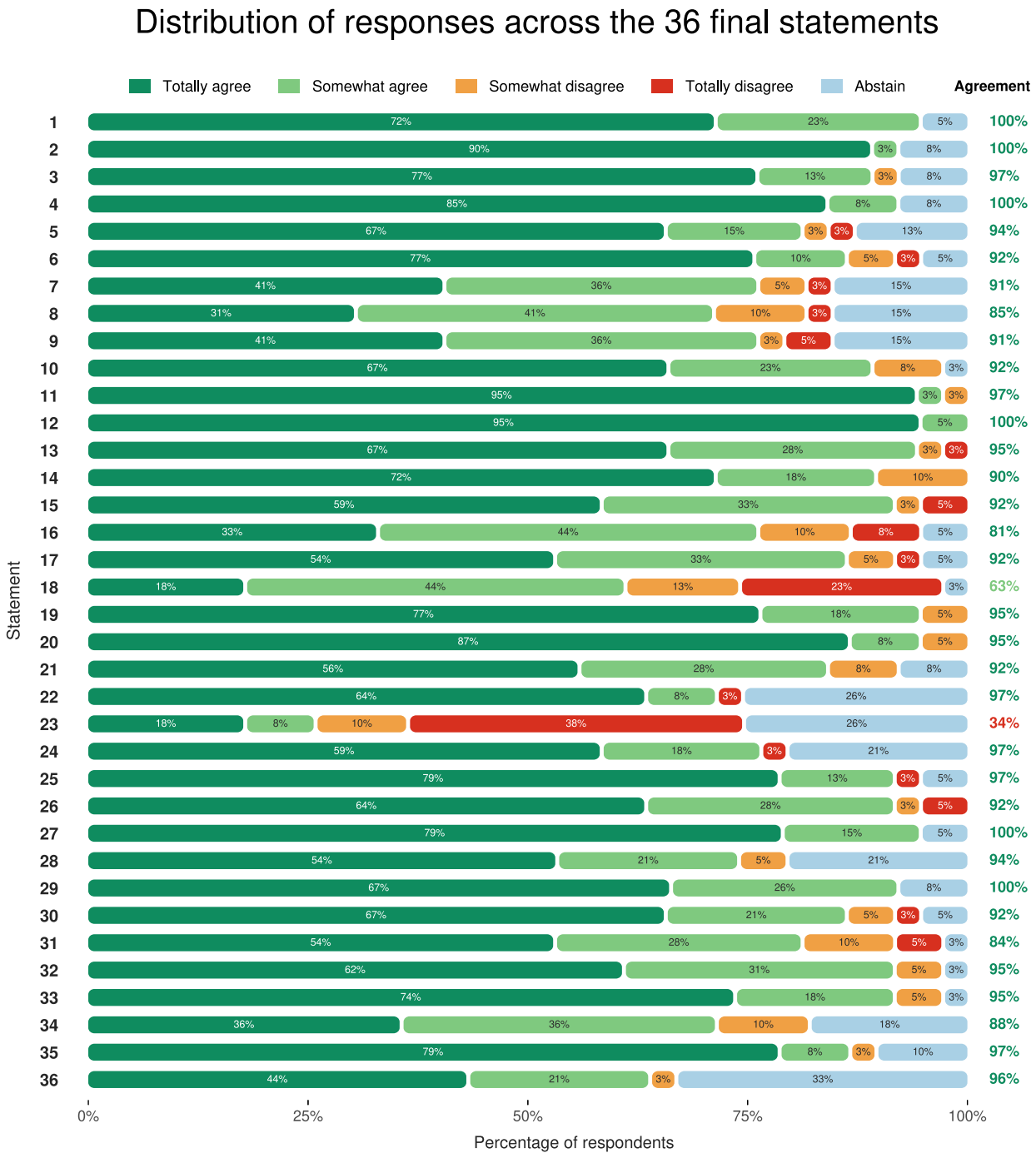


Fig. 1. Distribution of responses across the 36 final EPA2 Delphi statements.
For each statement, the horizontal bar shows the proportion of respondents in each response category: totally agree (dark green), somewhat agree (light green), somewhat disagree (orange), totally disagree (red) and abstain (light blue). The percentage of respondents in each category is reported inside the corresponding chip. The right-hand column reports the percentage of agreement among non-abstaining panellists.

the framing of the statements was necessarily influenced by the collective discussion that preceded it. The distribution of the votes nonetheless argues against a uniform conformity effect: explicit disagreement was recorded for 30 of the 36 statements, 107 dissenting votes were cast overall, abstention was used on 28 statements, and one statement submitted to the panel was rejected outright, indicating that panellists were willing to vote against proposals put before them. Second, the exercise was limited to two rounds, and the second round was applied only to the statements that had not reached strong agreement, so that the stability of opinion across rounds could not be assessed for the statements endorsed at the first round. Third, the writing committee was not independent of the voting panel. These choices were deliberate, and were made to keep the exercise anchored to the operational questions actually raised by the participating societies and to produce guidance within a timeframe compatible with the introduction of the two drugs into Italian clinical practice. They nonetheless limit the extent to which this exercise corresponds to a Delphi consensus in the classical sense, and the document is best understood as a structured expert consensus in which the degree of agreement on every statement is quantified and reported in full.

The EPA2 recommendations should be understood as a living framework. They define the minimum conditions for safe

implementation today, while identifying the areas in which evidence is likely to change rapidly: plasma biomarkers, amyloid PET timing, ARIA prediction models, treatment discontinuation rules and real-world measures of benefit. The next phase must be supported by national registries, shared minimum datasets, quality-controlled biomarker laboratories, standardised MRI reporting and transparent regional accreditation. Only through this coordinated infrastructure will Italy be able to move from regulatory availability to appropriate, equitable and sustainable use of disease-modifying therapies for Alzheimer's disease.

Ethical statement

This position paper does not require formal Health Ethical Approval, as it does not report data collected from individual patients.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors used Claude (Anthropic) solely for language proofreading and editing of the manuscript. The tool was not used to generate, analyse, or interpret data, nor to formulate scientific content. All authors reviewed and approved the final text and take full responsibility for its content.

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CRediT authorship contribution statement

Alberto Benussi: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Visualization, Project administration, Writing – original draft, Writing – review & editing. **Federica Agosta:** Methodology, Validation, Investigation, Writing – review & editing. **Luisa Agnello:** Investigation, Writing – review & editing. **Alba Rosa Alfano:** Investigation, Writing – review & editing. **Mattia Altini:** Investigation, Writing – review & editing. **Antonio Antico:** Investigation, Writing – review & editing. **Stefania Basilico:** Investigation, Writing – review & editing. **Giuseppe Bellelli:** Investigation, Writing – review & editing. **Laura Bonanni:** Investigation, Writing – review & editing. **Gabriella Bottini:** Investigation, Writing – review & editing. **Marco Bozzali:** Methodology, Validation, Investigation, Writing – review & editing. **Ovidio Brignoli:** Investigation, Writing – review & editing. **Giuseppe Bruno:** Investigation, Writing – review & editing. **Annachiara Cagnin:** Investigation, Writing – review & editing. **Sonia Francesca Calloni:** Investigation, Writing – review & editing. **Stefano F. Cappa:** Investigation, Writing – review & editing. **Filippo Caraci:** Investigation, Writing – review & editing. **Diego Cecchin:** Investigation, Writing – review & editing. **Marcello Ciaccio:** Investigation, Writing – review & editing. **Sirio Cocozza:** Investigation, Writing – review & editing. **Mirco Cosottini:** Investigation, Writing – review & editing. **Diego De Leo:** Investigation, Writing – review & editing. **Andrea Falini:** Investigation, Writing – review & editing. **Lorenzo Gaetani:** Investigation, Writing – review & editing. **Nicoletta Gandolfo:** Investigation, Writing – review & editing. **Fabio Gotta:** Investigation, Writing – review & editing. **Raffaele Lodi:** Investigation, Writing – review & editing. **Giancarlo Logroscino:** Investigation, Writing – review & editing. **Elena Marcello:** Investigation, Writing – review & editing. **Camillo Marra:** Investigation, Writing – review & editing. **Walter Marrocco:** Investigation, Writing – review & editing. **Silvia Morbelli:** Investigation, Writing – review & editing. **Patrizia Mecocci:** Investigation, Writing – review & editing. **Enrico Mossello:** Investigation, Writing – review & editing. **Lorenzo Palleschi:** Investigation, Writing – review & editing. **Pasquale Palumbo:** Investigation, Writing – review & editing. **Leonardo Pantoni:** Investigation, Writing – review & editing. **Lucilla Parnetti:** Investigation, Writing – review & editing. **Luca Roccatagliata:** Investigation, Writing – review & editing. **Sandro Sorbi:** Investigation, Writing – review & editing. **Patrizia Spadin:** Investigation, Writing – review & editing. **Alessandra Splendiani:** Investigation, Writing – review & editing. **Alessandro Tessitore:** Investigation, Writing – review & editing. **Andrea Ungar:** Investigation, Writing – review & editing. **Giuseppe Zappalà:** Investigation, Writing – review & editing. **Alessandro Padovani:** Conceptualization, Methodology, Investigation, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Luisa Agnello reports no conflicts of interest. Federica Agosta is Associate Editor of NeuroImage: Clinical and European Journal of Neurology and has received speaker honoraria from Biogen Idec, Bristol Myers Squibb, Eisai, Eli Lilly, GE Healthcare, Neuraxpharm, and Roche, and editing fees from Elsevier; she received research support from the Italian Ministry of Health, the Italian Ministry of University & Research, AriSLA, the European Research Council, and the Foundation for Alzheimer's Research. Alba Rosa Alfano reports no relevant conflicts of interest. Mattia Altini reports no conflicts of interest. Antonio Antico reports no conflicts of interest. Stefania Basilico reports no conflicts of interest. Giuseppe Bellelli has received research funding from the Italian Ministry of Health and University, and has received speaker honoraria from Eli Lilly, PIAM, GSK, Italfarmaco, Nestlé and Damor. Alberto Benussi has received speaker honoraria from Angelini Pharma, Eli Lilly, Novo Nordisk and has served at scientific advisory boards for Eisai and Eli Lilly; he received research grants from Airalzh, Fondazione Cariplo, the Fondation pour la Recherche sur Alzheimer, and the Italian Ministry of University & Research; he is listed as an inventor on issued patents on the use of non-invasive brain stimulation for the differential diagnosis of dementia and to increase cognitive functions in patients with neurodegenerative disorders. Laura Bonanni reports grants from the Italian Ministry of Health, the Italian Ministry of Education, and Eli Lilly; consulting fees from Eli Lilly; honoraria for lectures from GE Healthcare and Eli Lilly; and support for meeting attendance from scientific societies. Gabriella Bottini reports no conflicts of interest. Marco Bozzali has received speaker honoraria from Eli Lilly. Ovidio Brignoli reports no conflicts of interest. Giuseppe Bruno reports no conflicts of interest; he received financial compensation from Eli Lilly for participation on the GERAS advisory board. Annachiara Cagnin has received consulting fees and/or speaker honoraria from Eli Lilly, Biogen, Eisai, Roche, PIAM, Novo Nordisk and Lundbeck, and research support from the Italian Ministry of Health and Regione Veneto. Sonia Francesca Calloni reports no conflicts of interest. Stefano F. Cappa reports no conflicts of interest. Filippo Caraci was Principal Investigator of an investigator-initiated research project on vortioxetine funded by Lundbeck, served as consultant for advisory board from Angelini, Eisai and he has given lectures for Eisai, Lundbeck and Eli Lilly. Diego Cecchin received speaker and advisory board honoraria from Eli Lilly, GE Healthcare and Life Molecular Imaging. Sirio Cocozza has served on an Amicus

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100685.

Data availability

Anonymised individual responses to the Delphi questionnaire are available from the corresponding author upon reasonable request. The full set of statements and the corresponding agreement levels are reported in Table 1, and the corresponding distribution of votes is illustrated in Fig. 1.

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