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Original article

## Adapting the spanish healthcare system for disease-modifying treatments in early-stage alzheimer's disease

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## ABSTRACT

**Background:** The emergence of disease-modifying therapies targeting amyloid pathology represents a major paradigm shift in the management of Alzheimer disease (AD). However, their implementation poses substantial organizational, infrastructural, and clinical challenges for health systems.

**Objectives:** To identify the key challenges and establish priority recommendations for the effective incorporation of amyloid-targeting therapies into the Spanish National Health System.

**Design, Setting, and Participants:** This multiphase consensus study was conducted within the Spanish National Health System between September 2024 and July 2025. The study comprised a narrative literature review, qualitative research, regional workshops, and a modified RAND/UCLA Delphi process. A total of 56 experts participated, including a scientific committee of 6 Alzheimer disease specialists and an expert panel of 50 multidisciplinary professionals involved in AD care.

**Measurements:** Identification of key challenges across the AD care pathway; development, evaluation, and prioritization of consensus-based recommendations; and estimation of patient demand, including projected increases in day hospital activity and magnetic resonance imaging utilization.

**Results:** Ten key challenge areas were identified, encompassing early detection and referral, diagnostic confirmation, assessment of patient eligibility, treatment administration in day hospitals, monitoring of amyloid-related imaging abnormalities, evaluation of treatment effectiveness, infrastructure and capacity, professional training, patient information and support, and health care planning. Of the 43 recommendations assessed, 38 were rated as appropriate and necessary, with 14 prioritized for immediate implementation. Demand estimation models indicated that 11 to 26 patients per 100,000 inhabitants could be treated under current care patterns, increasing to 17 to 115 per 100,000 inhabitants under alternative eligibility scenarios.

**Conclusions:** This consensus defines the clinical, organizational, and infrastructural requirements necessary to integrate amyloid-targeting therapies into routine care within the Spanish National Health System. The prioritized recommendations define immediate actions to address the challenges identified and may serve as a reference for other health systems facing similar implementation processes.

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**Abbreviations**

- ad (alzheimer's disease)
- apoe4 (apolipoprotein e 4)
- aria (amyloid-related imaging abnormalities)
- atts (amyloid-targeting therapies)
- csf (cerebrospinal fluid)
- ema (european medicines agency)
- fda (Food and Drug Administration)
- MCI (mild cognitive impairment)
- MRI (magnetic resonance imaging)
- PET (positron emission tomography)

**1. Introduction**

Alzheimer's disease (AD) is the leading cause of dementia and the most common neurodegenerative disorder worldwide. It accounts for up to 60%–80% of all dementia cases and is a major global health challenge [1]. Dementia leads to increased morbidity, mortality, disability, and dependence, resulting in a significant loss of quality of life and reduced life expectancy [2]. Global prevalence is projected to reach 135 million by 2050, a situation that will generate a significant burden for healthcare systems [3].

The advent of disease-modifying treatments (DMTs) in the form of

amyloid-targeting therapies (ATTs) heralds a major paradigm shift in AD therapeutics [4]. These monoclonal antibodies (mAbs) are the first to demonstrate a slowing of clinical decline by targeting the underlying biological mechanisms of AD, and the approval of lecanemab and donanemab for early-stage disease has redefined the therapeutic landscape of the disease [5].

The introduction of ATT therefore represents a therapeutic breakthrough, but it also poses a major challenge for health systems worldwide [3,6–10]. Careful reorganization of early detection, diagnosis and management processes will be needed, and new care models and clinical pathways must be developed for the safe and efficient delivery of mAbs to eligible patients [3].

Modeling studies underscore the value of forecasting demand for eligibility assessments, biomarker testing, and treatment delivery infrastructures. Quantifying the healthcare resources required to administer ATTs is critical to guarantee fair access and agile delivery and facilitate proactive system planning and policy development [9]. This approach also creates a framework for coordinated health system planning and resource allocation for ATTs in AD, supporting policy-makers and clinicians in ensuring proper provision of care in clinical practice [8,9].

Local infrastructures must adapt to ensure resource availability and effective and equitable delivery [3,8,9]. The ALMA-CARE project was

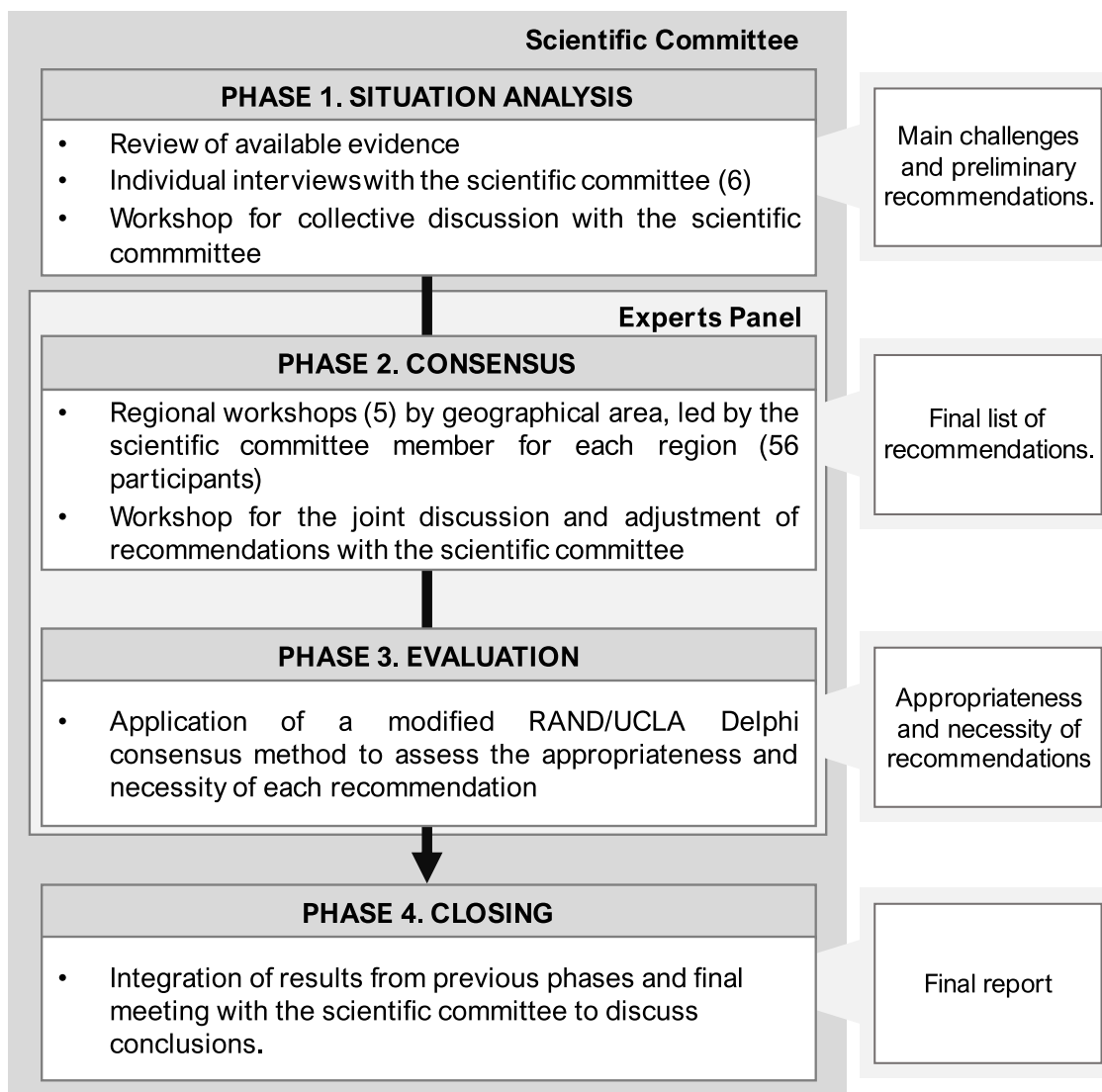


Fig. 1. ALMA-CARE methodology.

conceived as a national consensus initiative to identify the key challenges and priorities to incorporate mAbs into the Spanish national health system, a decentralized public healthcare system offering universal coverage that transfers healthcare competences to the autonomous regions. This decentralized organization may result in variability in care delivery and access to resources across regions, underscoring the relevance of achieving national consensus to guide coordinated and equitable implementation. The experience and methodology developed through ALMA-CARE are expected to foster dialogue among stakeholders to address barriers to the timely delivery of AD therapies in Spain. Our recommendations may also serve as a reference for other health systems facing similar challenges.

The consensus presented in this article has been officially endorsed by the Spanish Society of Neurology (SEN) and the Spanish Society of Neuroradiology (SENR).

## 2. Methods

This study consisted of 4 consecutive phases (Fig. 1) implemented between September 2024 and July 2025. A total of 56 experts participated at 2 levels of involvement.

The scientific committee comprised 6 specialist physicians, 5 neurologists and 1 neuroradiologist, all of whom had extensive experience in Alzheimer's disease (AD) clinical care and research. The committee participated in all study phases, defined the methodological framework, and oversaw the interpretation of the results. The expert panel comprised 50 health professionals from different healthcare settings and regions in Spain. Participants were selected through purposive sampling based on predefined criteria, including clinical expertise in early-stage AD, involvement in multidisciplinary units specialized in cognitive diseases or hospital-based services with demonstrated experience in AD care, and/or holding key roles within the care pathway potentially affected by the introduction of DMTs. Several members of the panel have participated in ATTs clinical trials, but prior experience with ATTs was not required for inclusion. The scientific committee identified potential participants to ensure balanced representation across specialties, levels of care, and geographic areas within the decentralized Spanish National Health System, a universal, tax-funded and decentralized system organized across primary care and specialized hospital-based services and managed by the 17 Autonomous Communities within a common national framework.

Most invited experts agreed to participate. When an initially contacted professional was unable to participate, a substitute with comparable expertise from the same specialty or healthcare setting was identified to preserve balanced representation. The panel included neurologists (n = 25), neuroradiologists (n = 8), geriatricians (n = 5), family and community medicine physicians (n = 4), nuclear medicine specialists (n = 4), nurses (n = 4), psychiatrists (n = 3), hospital pharmacists (n = 2) and an emergency medicine physician (n = 1) (*Supplementary Material*, Table S1). An external consultant was contracted to give methodological advice and coordinate and facilitate the study.

In the first phase, the status of AD care was analyzed on the basis of a narrative review of the literature and individual semi-structured interviews with members of the scientific committee.

The narrative review aimed to identify clinical, organizational, and infrastructural challenges related to the implementation of ATTs in early-stage AD. Searches were conducted in PubMed/MEDLINE and relevant regulatory and institutional websites (e.g., EMA, FDA, Alzheimer's Association, Spanish Ministry of Health) covering the last ten years. Search terms included combinations of: "Alzheimer's disease", "early-stage Alzheimer's disease", "mild cognitive impairment", "amyloid-targeting therapies", "anti-amyloid monoclonal antibodies", "disease-modifying treatments", "health system preparedness", "care pathways", "healthcare capacity", "biomarkers", and "amyloid-related imaging abnormalities (ARIA)". Eligible sources included clinical practice guidelines, consensus statements, regulatory documents,

preparedness analyses, and modeling studies. The initial literature search was conducted at the start of the study in September 2024. Throughout the study and until manuscript finalization, additional relevant publications were incorporated on an ad hoc basis, including those identified through expert recommendation and newly published evidence.

Six individual semi-structured interviews (approximately 90 min each) were conducted using a predefined interview guide (*Supplementary Material*, Table S2). The interviews, documented through transcripts, revolved around the organization and phases of the care process and the availability of resources, the aim being to pinpoint key factors in the introduction of new treatments.

The synthesis of findings from the narrative review and the interviews served as the basis for two subsequent workshops organized by the scientific committee. The objective of the first was to compare the current situation with an ideal future scenario, identify the main challenges, and draw up preliminary recommendations for further discussion and consensus. The aim of the second workshop was to develop a model to estimate the number of candidates for ATTs, taking into account the current demand estimated by the committee and the potential demand based on the evidence available in the literature. This model was also used to calculate additional resources needed for day hospitals and magnetic resonance imaging (MRI).

In the second phase, the preliminary recommendations developed by the scientific committee were circulated to all members of the expert panel for individual review. Subsequently, five regional workshops were organized (north, south, east, center and west of Spain), each led by a member of the scientific committee. During these sessions, panelists discussed the recommendations collectively, provided structured feedback, and identified regional specificities that could influence their implementation.

The conclusions of the regional workshops were synthesized and presented to the scientific committee in a workshop where the panel's inputs were reviewed and a final list of updated recommendations was drawn up.

In the third phase, the scientific committee and the expert panel took part in a modified Delphi RAND/UCLA process to reach consensus on the final list of recommendations using an online structured questionnaire [11]. The Delphi exercise was conducted as a single-round modified RAND/UCLA process, as the recommendations had already been extensively discussed and refined during prior scientific committee meetings and five regional workshops. Considering the novelty and complexity of ATT implementation in AD, in-person deliberative discussions were deemed more appropriate and enriching for addressing uncertainties, incorporating diverse regional perspectives, and achieving convergence before the formal consensus scoring. The subsequent structured Delphi round therefore served to formally validate and quantify the level of agreement on recommendations that had already undergone substantial qualitative refinement. Each recommendation was evaluated in terms of appropriateness and necessity in a single round using a Likert ordinal scale of 1 to 5 points. The response categories were divided into 3 levels (1–2: inappropriate or unnecessary; 3: neither for nor against, unclear; 4–5: appropriate or necessary). Participants were invited to make comments and observations on each recommendation.

A recommendation was considered appropriate if its implementation would contribute positively to the incorporation of ATTs in the health system and/or foster an optimal healthcare environment for their use, regardless of the cost. A recommendation was considered necessary when, in addition to being considered appropriate, failure to implement it would significantly hinder the use of these treatments and obstruct patient access to them within the health system or if the expected benefit outweighs the potential barriers or costs.

Panelists were not allowed to exchange information during the process, and unscored recommendations were treated as missing data for statistical purposes. Data were analyzed using Microsoft Excel,

calculating the median, mean, interquartile range and standard deviation to classify the degree of appropriateness, necessity and agreement of the responses (*Supplementary Material*, Table S3). Agreement was considered to be reached when at least 77% of panelists scored within the range containing the median (1–2, 3, or 4–5). Priority recommendations were defined using an operational threshold of a mean score greater than 4.5 for both appropriateness and necessity, reflecting a high level of agreement.

In the fourth phase, the scientific committee organized a workshop to integrate the results of the previous phases. The statistical outcomes of the Delphi process and qualitative panel feedback were reviewed to synthesize key findings and consolidate the final conclusions of the consensus.

### 3. Results

#### 3.1. Challenges and recommendations

The in-depth analysis of the AD care pathway in Spain, which generally involves initial evaluation in primary care followed by referral to specialized hospital-based services for diagnostic confirmation and management, identified 10 key challenges related to the implementation of ATTs, structured according to its different stages (*Supplementary Material*, Figure S1).

Early detection and appropriate referral of patients, together with a clear definition of the roles of primary care physicians and neurologists during the initial assessment, were identified as the first challenge. The second challenge involved access to additional testing and coordination of the diagnostic process in the hospital setting. The third challenge after confirming the diagnosis is to evaluate the patient's profile and determine their eligibility for ATT, according to the criteria established in the prescribing information.

The fourth challenge is how to reconcile the structural and logistical needs associated with the delivery of treatment in day hospitals, the capacity of these facilities, and the availability of professionals. Monitoring the risk of amyloid-related imaging abnormalities (ARIA) and evaluating therapeutic efficacy with clinical and radiological follow-up constitute the fifth and sixth challenges.

Effective delivery of the new treatments requires sufficient infrastructure, adequate resources and specifically trained professionals; these comprise the seventh and eighth challenges, while the need for providing guidance and support to the patient and their circle is defined as the ninth challenge.

Finally, strategic planning and coordination needed to integrate all these elements in the health care system comprise the tenth challenge.

A total of 43 recommendations structured around the 10 key challenges raised were assessed using the Delphi method. Of the 43 recommendations, 38 were considered appropriate and necessary, and of these, 14 were priorities (Table 1). The five recommendations that did not reach consensus are presented in Table S4 of the *Supplementary Material*.

Overall, 55 experts participated in the Delphi round, representing 98.2% of the total panelists. Detailed scores for each recommendation are provided in Table S5, together with a grid summarizing mean appropriateness and necessity ratings in Figure S2 of the *Supplementary Material*.

#### 3.2. Estimated demand and resources

The demand model comprises two complementary approaches, reflecting current care demand (Model 1) and estimating potential future demand (Model 2).

The first model (Fig. 2, Model 1) was constructed from the clinical experience of the scientific committee and the healthcare data of patients currently seen by neurologists. It showed that between 11 and 26 patients per 100,000 inhabitants could be treated with the new

therapies, according to current care demands.

The second model (Fig. 2, Model 2) shows an updated estimate based on the prevalence of mild cognitive impairment (MCI) and new patients who might request evaluation and treatment, once DMTs become available (J. Escudero, data presented at the LXXV Meeting of the SEN – *Grupo de Conducta y Demencias* (Behavior and Dementia Group), Valencia, Nov 1, 2023; data not published). Model 2 proposes 3 possible eligibility scenarios in which 5%, 7% or 20% of patients are potential candidates for treatment, resulting in an estimated range from a minimum of 17 to a maximum of 115 patients per 100,000 inhabitants.

It should be noted that this model is not intended to provide an accurate calculation of demand, but rather to serve as a guide to adjust the available resources and progressively prepare the health system.

Using the figures estimated in both models, the infusion frequency stated in the prescribing information and MRI requirements from clinical trials as a reference, a projection was made for the expected increase in day hospital traffic and demand for MRI procedures (Table 2).

### 4. Discussion

The results of the ALMA-CARE consensus coincide with previous reports on the preparation of health systems for the launch of ATTs [3, 10]. Care systems must be reorganized, and clinical pathways and health infrastructures must be adapted for the introduction of mAbs. The main needs include greater diagnostic capacity, improved access to biomarker testing and neuroimaging resources, and specific training for the professionals involved [4,12].

Studies have already been published in Spain on the degree of knowledge and awareness of neurology departments facing the imminent launch of new treatments [8]. The ALMA-CARE consensus expands on this process by analyzing the organizational and operational readiness of various key specialties involved in the delivery of new therapies.

The ALMA-CARE consensus aims to be used as a reference that, in line with international initiatives [13–16] can help plan and adapt healthcare systems for the future, taking into account local organizational models and available resources. The aim is to foster equitable access to ATTs and timely and safe treatment of patients with early-stage AD.

The discussion addresses the main challenges mentioned above and focuses on the priority recommendations that inform the most immediate actions included in the proposed roadmap.

#### 4.1. Role of primary care physicians and neurologists in symptom detection and initial assessment

Early diagnosis of AD and other types of dementia is essential to begin therapeutic interventions, plan care, reduce the social and health burden of the disease, and initiate treatment before the development of more advanced phases when options are more limited [17,18]. It is essential to raise awareness, not only among health professionals involved in the early identification of symptoms, but also among patients and their families [13]. In many cases, family members are the first to detect cognitive impairment and encourage patients to present in early stages, before symptoms become patent [17].

Building awareness should be go hand in hand with continuous training to enable physicians to promptly detect signs of cognitive impairment and use appropriate tools to screen for early-stage AD. Primary care physicians should use specific cognitive tests, supplemented with questionnaires completed by family or close contacts, to improve detection of MCI [19,20], which remains an unmet need in current practice. The sensitivity and specificity of the main screening tests for MCI differ [21,22], and expert opinions vary on the limitations of some of the most widely used tests, such as MoCA and MMSE. This reinforces the need for local consensus, understood as a coordinated agreement between primary care centers and their reference neurology services to select the most appropriate screening tools, based on

**Table 1**

Recommendations for preparing the Spanish healthcare system for the introduction of new treatments for Alzheimer's disease.

Challenge 1: Early symptoms and initial assessment: primary care and general neurology		
N	Recommendation	Result
1	<b>Raise awareness among healthcare professionals, particularly in the fields of primary care, neurology, internal medicine, psychiatry, geriatrics, as well as patients and their families, about the importance of early detection and diagnosis.</b>	<b>Appropriate and necessary Priority</b>
2	Strengthen human resources in primary care, evaluate the establishment of the figure of the reference professional in cognitive impairment to facilitate close collaboration with hospital care during the initial assessment and diagnostic confirmation, and involve nursing professionals in the identification of early-stage AD.	Appropriate and necessary
3	<b>Ensure continuous medical education for primary care teams, general neurology, psychiatry, geriatrics, internal medicine, and other specialties involved, in the early identification of symptoms and/or signs that may indicate the onset of cognitive decline (subjective complaints, mild cognitive impairment, dementia), and on tools for the identification and screening of early-stage AD (e.g., specific cognitive tests or clinically validated biomarkers).</b>	<b>Appropriate and necessary Priority</b>
4	Conduct valid cognitive tests to detect mild cognitive impairment from primary care teams (in questionnaire format or through digital tools) to identify early AD, according to the characteristics and population of each health area.	Appropriate and necessary
5	Select screening tests by consensus between primary care and hospital care, according to the characteristics and population of each health area.	Appropriate and necessary
7	Perform a consultation with the neurologist in cases of high clinical suspicion of mild cognitive impairment, even when the screening tests are normal. Clinical judgment should prevail over specific test scores, and each case should be evaluated individually.	Appropriate and necessary
8	<b>Develop an agile referral pathway from primary care for potential candidates for ATTs, establishing specific referral criteria that are adaptable to the particularities of each healthcare area or department.</b>	<b>Appropriate and necessary Priority</b>
Challenge 2: Hospital assessment and diagnostic confirmation		
10	<b>Implement and ensure validated biomarkers for the diagnosis of AD in the hospital setting, including cerebrospinal fluid biomarkers (p-tau 181/A<math>\beta</math>42, t-tau/A<math>\beta</math>42, A<math>\beta</math>42/40), amyloid PET (A<math>\beta</math>) and/or plasma biomarkers.</b>	<b>Appropriate and necessary Priority</b>
11	Plasma biomarkers should be determined in specialized neurological care, in line with the recommendations of the Spanish Society of Neurology (SEN).	Appropriate and necessary
12	<b>Ensure the availability of appropriate tools for diagnosing dementias other than AD, including neuropsychological studies and structural and functional neuroimaging tests.</b>	<b>Appropriate and necessary Priority</b>
13	Develop and establish rapid in-hospital circuits to establish diagnosis and eligibility criteria for ATTs.	Appropriate and necessary
14	Promote the development of Multidisciplinary Committees for the evaluation of patients who are candidates for ATTs.	Appropriate and necessary
15	<b>Provide ApoE4 genotyping for patients who are potential candidates for ATTs.</b>	<b>Appropriate and necessary Priority</b>
Challenge 3: Candidate patient profile		
16	<b>Use ATTs according to prescribing information criteria for the selection of candidate patients, also taking into account clinical practice guidelines that may be developed by medical societies.</b>	<b>Appropriate and necessary Priority</b>
Challenge 4: Treatment: day hospital and infusion		
17	<b>Prepare day hospitals for the administration of these treatments.</b>	<b>Appropriate and necessary Priority</b>
Challenge 5: Follow-up: monitoring the risk of ARIA		
18	<b>Use 2D or 3D FLAIR, GRE and DWI sequences for the detection of ARIA-E and ARIA-H in patients treated with ATTs. Additionally, consider the complementary use of SWI (susceptibility-weighted imaging) sequences.</b>	<b>Appropriate and necessary Priority</b>
19	<b>Provide sufficient human resources for the efficient use of magnetic resonance imaging (MRI) machines.</b>	<b>Appropriate and necessary Priority</b>
21	Plan and schedule all MRIs (baseline and follow-up) prior to treatment, ensuring that they are always performed on the same, preferably high-field, machine.	Appropriate and necessary
22	<b>Develop and establish consensus protocols between neurology, neuroradiology, and emergency departments for monitoring the safety of ATTs. These protocols should include, at a minimum, referral and assessment of patients with suspected ARIA in an emergency department by an on-call neurologist and, in the case of patients with severe symptoms, priority MRI within the first 24h</b>	<b>Appropriate and necessary Priority</b>
23	Establish a system for identification of treated patients, available in primary care and hospital care. This system should include key information on treatment and alert to the risk of ARIA, thus facilitating rapid identification and appropriate care.	Appropriate and necessary
24	Include "patient under treatment with ATTs" in the stroke protocol checklist.	Appropriate and necessary
25	<b>Establish an anticoagulation alert in electronic prescribing systems for patients treated with ATTs.</b>	<b>Appropriate and necessary Priority</b>
26	Design and implement a training program adapted to each professional profile (neurology, radiology, primary care, emergency, intensive care units, advanced practice nursing, etc.) for the identification and management of ARIAS and other side effects, including specific training in existing protocols and circuits.	Appropriate and necessary
27	Incorporate key professional profiles for the identification and management of ARIAs and other adverse effects, such as on-call neurology and neuroradiology specialists, specialized nurses and case managers.	Appropriate and necessary
Challenge 6: Follow-up: monitoring treatment efficacy		
28	<b>Protocolized collection and collection of real-life data on safety and efficacy including possible surrogate markers in patients treated with ATTs.</b>	<b>Appropriate and necessary</b>

Challenge 7: Infrastructure, resources and capacity		
29	Estimate the expected patient demand to determine the impact of new treatments will have on AD (see Fig. 2).	Appropriate and necessary
30	Analyze the care burden in primary care and hospital care derived from the introduction of ATTs.	Appropriate and necessary
31	<b>Prepare all personnel, material, and organizational resources necessary to adequately care for patients (see Fig. 3).</b>	<b>Appropriate and necessary</b>
32	Determine the most efficient healthcare organization for the incorporation of new treatments taking into account the specific needs of each center or healthcare area.	Appropriate and necessary
33	<b>Adjust available human and material resources, especially those considered critical, such as neurology, neuroradiology, day hospital, and MRI equipment, for the implementation of new treatments for AD (see Fig. 3).</b>	<b>Appropriate and necessary</b>
Challenge 8: Healthcare professionals and training		
34	Develop and implement training programs adapted to each professional profile: cognitive impairment, screening and selection of patients, identification and management of adverse effects, referral and prioritization circuits, neuroimaging, and others.	Appropriate and necessary
35	Incorporate the following professional profiles in the early AD care process (MCI or mild dementia): case management, advanced practice nursing, neuroradiology, professionals with the ability to perform neuropsychological assessments, nuclear medicine, and others.	Appropriate and necessary
36	Develop joint protocols for coordination and collaboration between levels of care and specialties for the management of these patients, especially between PC, neurology, neuroradiology and the emergency department.	Appropriate and necessary
Challenge 9: Patient information and support		
37	Design an information process for patients and their circle that includes the potential risks of the available treatments and encourages spending the time needed in consultations for shared decision-making.	Appropriate and necessary
38	Prepare informative material (written, web-based, etc.) on ATTs: detailed description, possible complications and adverse effects.	Appropriate and necessary
Challenge 10: Healthcare planning and care organization		
39	Update and budget for a <i>Comprehensive Plan for Alzheimer's and other Dementias</i> . This projection should address the introduction and sustained availability of ATTs, as well as availability of multidisciplinary units specialized in cognitive pathology, necessary human resources, including the incorporation of new profiles, necessary material resources, training programs for health professionals, schedules, and evaluation indicators.	Appropriate and necessary
40	Establish health plans in each autonomous community that set out the necessary resources to manage AD, including early-stage disease, and all items described in the previous point.	Appropriate and necessary
42	Establish multidisciplinary units specializing in cognitive diseases and provide them with the necessary resources to guarantee equitable access to ATTs for all patients.	Appropriate and necessary

experience, available resources and characteristics of the population served. Nevertheless, the clinical judgment of the physician and the combined use of additional tools should always prevail, especially when mild or atypical disease is suspected.

The panel recommends establishing agile referral circuits between primary care and memory or cognitive impairment clinics using clearly defined criteria for potential ATT candidates. Although there is general agreement in the literature on the need to harmonize referral protocols [3], implementation of these measures must take into account the care capacity and organization in each area, since the possibility of direct referral varies widely across the country.

#### 4.2. Hospital evaluation and diagnostic confirmation

Diagnostic confirmation in the hospital setting should be based on clinically validated biomarkers used to confirm AD pathophysiology. The approved prescribing information for both lecanemab [23] and donanemab [24] require confirmation of amyloidosis for the selection of patients who may be suitable for mAbs treatment.

The test most widely used in Spain is the determination of biomarkers p-A $\beta$ 42/40, tau181/A $\beta$ 42 or t-tau/A $\beta$ 42 in cerebrospinal fluid (CSF). This has become the reference standard for the confirmation of amyloid pathology [14,17,20] but equitable access in Spain may depend on the prevailing infrastructure, qualified health personnel, and professionals experienced in the clinical interpretation of the results.

Amyloid positron emission tomography (PET) has become significantly more available and practicable in recent years since the introduction of the INVEAT plan [25], AEMPS approval of 3 radiopharmaceuticals [26] and the progressive nationwide expansion of the cyclotron network [27,28]. However, improvements are still needed to guarantee consistent availability and accessibility across the country.

Plasma biomarkers are emerging as a promising tool that will improve access and accelerate screening pathways. In Spain, they are

still undergoing validation [20,29] but in the early stages of the care process they could be especially useful as an initial screening tool that can prioritize patients who need a more in-depth investigation of biomarkers in CSF or on PET [20,30]. Experts agree that these procedures should first be implemented in specialized settings under the supervision of experienced professionals [20]. This should in no way replace the continued use of standard diagnostic tools and close monitoring of the clinical situation of patients who are under evaluation for cognitive problems. This approach should facilitate decision-making and optimize access to more complex tests [30], and as scientific evidence is consolidated and practical experience is acquired, biomarker determination could be extended progressively to general neurology and even later to primary care, provided that close coordination is maintained with the hospital [20].

Other tools that guide the differential diagnosis of early-stage AD compared to other dementias and neurodegenerative disorders are also needed and should be available at the center.

#### 4.3. Candidate patient profile

The introduction of ATTs requires a standardized procedure for selecting suitable patients in line with the prescribing information [23, 24], which should also be reflected in clinical practice guidelines [18, 30–33]. In clinical practice, the candidate patient is usually one with early-stage AD, with no contraindicating concomitant diseases, who can comply with regular monitoring and tests to determine cerebral amyloid deposition. The prescribing information for ATTs approved by the European Medicines Agency (EMA) [23,24], the United States Food and Drug Administration (FDA) [34,35] and the British Medicines and Healthcare Products Regulatory Agency (MHRA) [36,37] lists a series of contraindications and precautions that underline the need for an individualized risk assessment before starting treatment. The most important are previous hemorrhagic lesions and the apolipoprotein E  $\epsilon$ 4

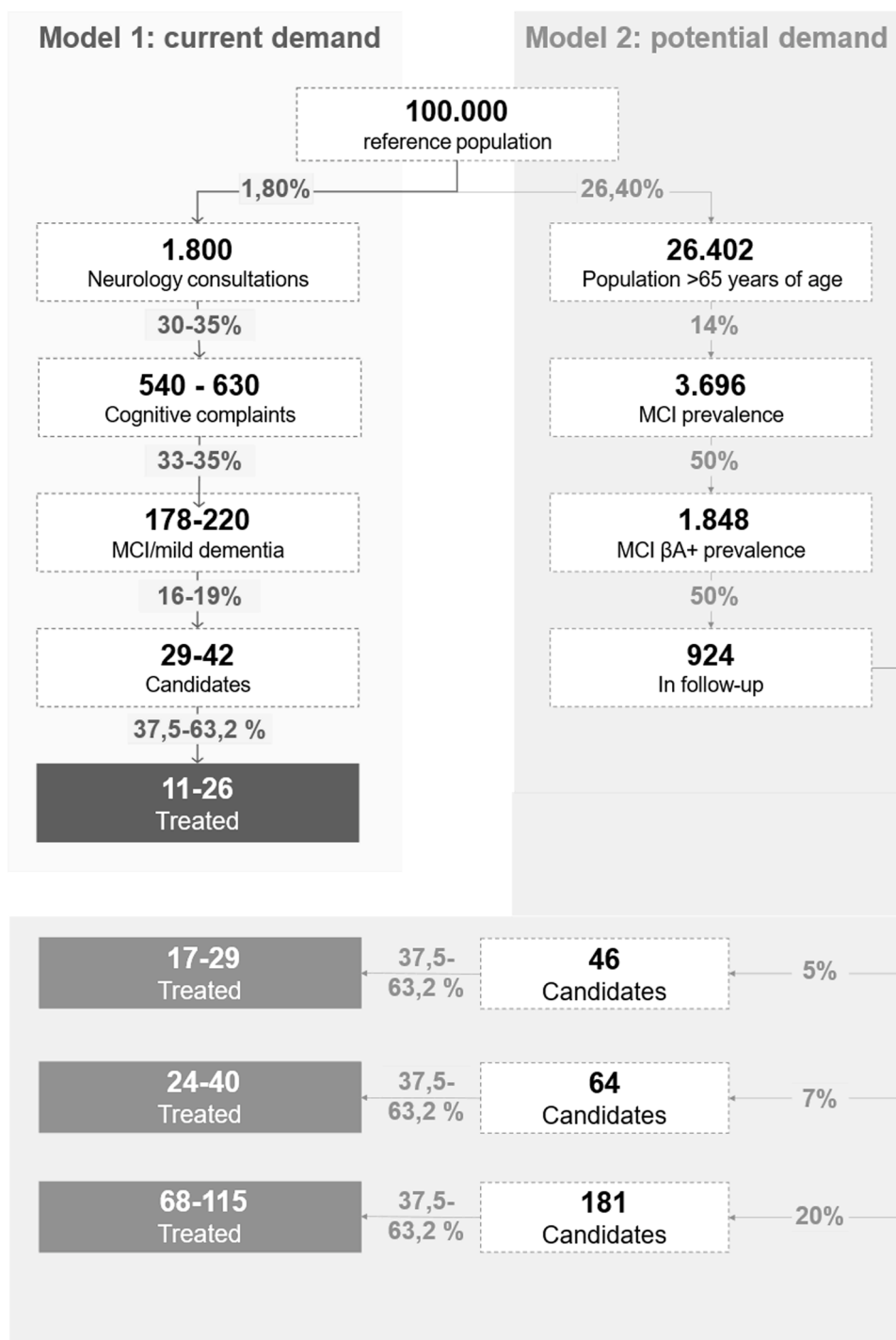


Fig. 2. Estimated patient demand.

\* All estimates are made on the basis of the experience of the expert panel (current panel) and the model presented at the LXXV Meeting of the SEN (potential demand).

(ApoE4) genotype. Baseline MRI should include fluid attenuated inversion recovery (FLAIR) and gradient echo (GRE) sequences, but for now, the exclusion criteria for microhemorrhages or superficial siderosis should be determined according to GRE. Susceptibility-weighted imaging (SWI) sequences are more sensitive, but the exclusion criteria based on SWI findings are still not validated, although it seems likely that guidelines will be put in place in the near future.

The EMA and MHRA have not approved the use of lecanemab and donanemab in homozygous patients for ApoE4 [23,24,36,37], although the FDA allows their use under a strict clinical and radiological

monitoring regimen [34,35]. Access to genotyping can be an additional barrier, not only for technical reasons, but also because of ethical, psychological, and clinical considerations. These tests should therefore be conducted with informed consent and appropriate genetic counseling in memory or cognitive impairment clinics, using standardized protocols [30].

Experts note that uncertainties persist regarding the technique to confirm amyloid pathology as a prerequisite for access to therapies after approval and funding of treatments in Spain. Existing validated techniques will probably be prioritized initially, followed by the progressive

**Table 2**  
Estimated resources.

	Day Hospital	Magnetic Resonance Imaging
Model 1 (11–26 treated patients)	<b>11 - 52</b> Additional patients/ month	<b>55 - 130</b> Additional patients/ month
Model 2 (17–115 treated patients)	<b>17 - 230</b> Additional patients/ month	<b>25 - 575</b> Additional patients/ month

The infusion schedules for donanemab (monthly) and lecanemab (twice monthly) were determined on the basis of the respective prescribing information. MRI requirements were derived from the pivotal trials: 1 MRI per year for donanemab and 4 MRIs per year for lecanemab. The ranges represent the minimum and maximum number of additional patients per month under each model, calculated according to the infusion and MRI requirements of both treatments.

If a patient develops symptoms suggestive of ARIA at any point during treatment, a clinical assessment including MRI must be performed. Additionally, in patients with ARIA, a follow-up MRI is required to assess resolution 2 to 4 months after the initial identification, to determine either resolution (ARIA-E) or stabilization (ARIA-H).

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introduction of plasma biomarkers. Scientific societies will play a key role in harmonizing diagnostic criteria and drawing up common criteria for the selection of candidate patients [20,29].

#### 4.4. Day hospital and infusions

The safe and efficient delivery of ATTs requires day hospitals with the equipment and human resources required to follow infusion protocols, monitor patients, and treat adverse effects. Although it is not mentioned in the recommendations, it is likely that well provisioned hospital pharmacies will also be essential for drug delivery.

In Spain, neurology day hospitals can either be independent or function as part of outpatient infusion facilities shared with other specialties, but in either case, the capacity for handling new indications is limited, and the use of not only spaces and time slots but also the increased need for staff experienced in infusion administration and the management of complications remains to be clarified [10]. Day hospitals in which ATTs are administered should be conceived as places for comprehensive and continuous care, with coordinated teams and personnel specially trained in administering these treatments, particularly in detecting and managing adverse reactions [3]. There is a risk that the system will not be able to sustain a steady turnover of infusions, and bottlenecks may form unless issues such as increased demand and the specific organization of AD care are addressed.

#### 4.5. Monitoring of ARIA risk

ARIA monitoring is one of the main challenges associated with the follow-up of patients treated with ATTs [16,38–40]. The most common radiological manifestations, vasogenic edema (ARIA-E) and microhemorrhages or cortical siderosis (ARIA-H), require close MRI monitoring and early clinical intervention if they appear [40].

The consensus is to use FLAIR sequencing to assess the extent and

evolution of vasogenic edema, and T2-GRE to identify and quantify areas of microhemorrhages and cortical siderosis. The systematic incorporation of diffusion-weighted sequencing (DWI) is useful to confirm the vasogenic nature of the edema and differentiate it from acute ischemic lesions that might require a modified clinical approach or contraindicate continued treatment. Moreover, the use of SWI is recommended whenever possible, as it is more sensitive than GRE for the detection of ARIA-H and superficial cortical siderosis and offers better diagnostic accuracy compared to conventional sequences [16,42].

If symptoms consistent with ARIA are detected, early coordinated intervention supported by clinical protocols shared with the neurology, neuroradiology and emergency departments should be initiated, ensuring rapid referral and an MRI performed within than 24 h [16], depending on the severity of symptoms. An easily incorporated priority action is to include anticoagulation alerts in the electronic prescription systems of emergency care programs, e.g., stroke code. Alert systems that are accessible from all care levels would facilitate the prompt activation of rapid pathways in the case of suspected adverse events and ensure effective communication among the teams involved.

In this respect, MRI is a critical resource, but merely installing new MRI equipment will not make up for a shortage of neuroradiologists and technicians. Similarly, allocating wider time slots for performing MRIs to absorb more MRI requests arising from the use of ATTs will not be helpful if the workforce is not expanded [8].

#### 4.6. Infrastructure, resources and capacity

The introduction of ATTs requires substantial changes in health infrastructure and care capacity. Without proper planning, waiting times and the burden of care can form bottlenecks that limit equitable access and effective care [6]. Ensuring the availability of the human, material and organizational resources needed for comprehensive care is key to the correct delivery of these treatments [8,10]. The resources identified in the ALMA-CARE consensus are listed in Fig. 3. Critical items are those for which high demand could generate significant limitations in clinical practice, especially those linked to neurology, radiology, day hospitals and MRI teams [8].

Experts agree on the need to design a realistic plan based on an accurate estimate of the candidate patient population, and to develop strategies to adapt the available resources, prioritizing areas with structural limitations or those that can be expected to experience greater care pressure in the initial years. The ALMA-CARE projections underline the specific need to bolster critical specialties, and to ensure the availability of imaging equipment and the continued operation of day hospitals. The provision of flexible organizational models adapted to the reality of each clinic or health area is essential to avoid bottlenecks and ensure the sustainability of the system.

Initially, the delivery and monitoring of ATTs will probably take place primarily in reference centers with specialized resources and referral pathways before being extended progressively and equitably throughout the country. However, the absence of standard criteria to define and assign specialized cognitive impairment units could lead to differences in structure, staffing, and capacity among centers, with the consequent threat to equitable access.

The successful delivery of ATTs will depend on the health system's ability to equitably scale, coordinate and strengthen critical resources that ensure safe, efficient and accessible care for all patients. Planning mechanisms should be flexible and adapted to the real-life situation of each health center or area and specifically address the availability and distribution of resources within the framework of a national strategy aimed at fostering efficiency, territorial equity and sustainability of the system.

#### 4.7. Professional training, patient support and healthcare planning

Although not prioritized as immediate actions compared with



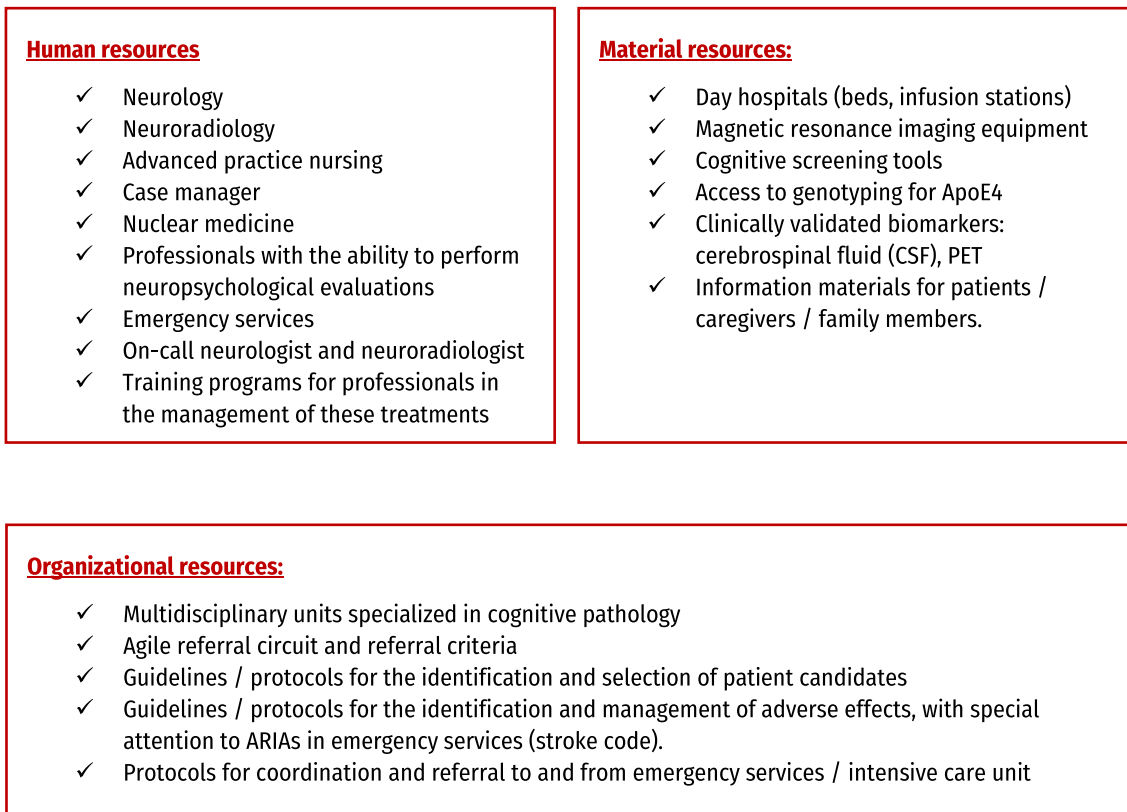


Fig. 3. Human, material and organizational resources needed.

diagnostic and infrastructural readiness, professional training, patient information, and healthcare planning were consistently rated as appropriate and necessary for the sustainable implementation of mAbs in early-stage AD. The consensus underscores the need for structured training programs adapted to different professional profiles, coordinated protocols across levels of care, and incorporation of key roles such as advanced practice nursing and case management. Clear information processes and shared decision-making are essential to support patients and families. Finally, updated national and regional planning frameworks, multidisciplinary cognitive units, and quality assurance mechanisms will be required to ensure equitable and consistent standards of care.

## 5. Conclusions

The ALMA-CARE consensus provides a framework for the integration of ATTs into the Spanish National Health System, identifying key challenges along the AD care pathway and defining priority actions to support their implementation.

The results highlight the need to optimize referral and diagnostic pathways, ensure appropriate candidate identification according to established criteria, guarantee access to validated biomarker testing, and implement standardized protocols for mAbs administration and safety monitoring. Strengthening infrastructure, allocating adequate human and technical resources, and promoting targeted training initiatives will be essential to achieve consistent and equitable implementation across regions.

The prioritized recommendations offer a practical roadmap to facilitate system readiness, promote equitable access, and optimize patient outcomes in the evolving therapeutic landscape of AD.

### 5.1. Limitations

Although multidisciplinary and geographic representation was sought, the number of participants was limited and may not fully reflect all regional organizational models within the Spanish National Health System. In addition, the Delphi evaluation was conducted in a single round using an adapted RAND/UCLA methodology, which may have reduced the opportunity for iterative refinement of agreement.

The demand model was conceived as a planning-oriented estimate based on expert input and published data, rather than as a formal epidemiological projection or cost analysis, and should therefore be interpreted accordingly. Finally, given the rapidly evolving regulatory and clinical landscape of DMTs for AD, future changes in eligibility criteria, biomarker implementation, and healthcare organization may influence the applicability of some recommendations over time. Prospective monitoring of implementation in routine clinical practice will be critical to assess the effectiveness of these recommendations and to guide future organizational adjustments.

### Data statement

The data that support the findings of this study are available from the corresponding author upon reasonable request, subject to institutional and ethical restrictions.

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

The authors declare that generative AI-assisted technologies (large language models) were used during the writing process exclusively for language editing, stylistic refinement, and improvement of clarity and readability of the manuscript. The use of these tools was limited and accounted for a minor proportion of the overall writing process (estimated at less than 10%), without generating scientific content, interpreting data, or influencing the study design, results, or conclusions. All content was critically reviewed, edited, and validated by the authors, who take full responsibility for the integrity and accuracy of the manuscript.

## CRediT authorship contribution statement

**R. Sánchez Valle:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Conceptualization. **A. Lleó Bisa:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Conceptualization. **A. Villarejo Galende:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Conceptualization. **E. Cuartero Rodríguez:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Conceptualization. **J. Escudero-Torrella:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Conceptualization. **N. Bargallo Alabart:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Conceptualization.

## Conflict of interest

RSV has received personal payments for participating in advisory committees or educational events for UCB, Wave, Roche Diagnostics, Ionis, NovoNordisk, Esteve and Almirall. Payments have been made to her facility for participation in Eisai clinical trials, and for participating in research projects, consulting, or educational events for Lilly. ALB reported receiving personal fees for service on advisory boards, or speaker honoraria from Almirall, Beckman-Coulter, Biogen, Eisai, Esteve, Fujirebio-Europe, Grifols, KRKA, Lilly, Novartis, NovoNordisk, Nutricia, Otsuka Pharmaceutical, Roche, and Zambón. ALB is co-author of a patent for synaptopathy markers in neurodegenerative disease (licensed to ADx, EPI8382175.0) and one on antibodies for amyloid precursor, methods and uses thereof, European priority (N°EP25382226). NBA has received personal payments for participation in advisory committees for Lilly, and for participation in educational events for Eisai, Lilly, and Siemens.

AVG has served as a consultant for Roche, Eli Lilly, Eisai, and Novo Nordisk. He has participated in educational activities sponsored by Novo Nordisk, Esteve, Almirall, GE Healthcare, KRKA, Alter, Schwabe, Organon, Roche and Zambon. ECR and JET report no conflicts of interest.

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We hope that this report will serve as a useful reference for health professionals, managers and decision makers in the field of health policies, both in Spain and in other countries, when designing efficient

equitable and sustainable care models in the new era of DMTs for AD.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100586.

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