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CONSENSUS STATEMENT

Blood-based biomarkers for Alzheimer's disease: positioning document and usage recommendations from the Behavioral Neurology and Dementia Study Group of the Spanish Society of Neurology

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Abstract
Introduction: The development of blood biomarkers for detecting Alzheimer's disease (AD) represents one of the most significant recent advances, and some are already available for clinical practice. Therefore, the Grupo de Estudio de Conducta y Demencias de la Sociedad

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Española de Neurología has formed a working group to review the current status and develop consensus recommendations for their clinical implementation.
Development: This document was prepared by neurologists from the Grupo de Estudio de Conducta y Demencias de la Sociedad Española de Neurología in two phases. First, a coordinating group defined the basic guidelines of the document, agreed on initial recommendations based on a literature review, and drafted a preliminary version. Subsequently, the proposal was reviewed by the entire working group, all comments were considered, and the coordinating group adjusted the recommendations until consensus was achieved among the participants.
Conclusions: The consensus document highlights the importance of early diagnosis of AD. It recommends interpreting blood biomarkers in the patient's clinical context, not in isolation. Specialized units can start using them, but this should be accompanied by ongoing research. More data are needed for their use in general neurology and primary care. Their use is not recommended in asymptomatic individuals, population screenings, or as direct-to-consumer tests. Public health systems should facilitate their implementation through appropriate funding to ensure equitable access. This document should be understood as an initial framework subject to periodic updates as new data emerge.

PALABRAS CLAVE
Biomarcadores sanguíneos;
Demencia;
Enfermedad de Alzheimer;
Diagnóstico precoz

Biomarcadores en sangre para la enfermedad de Alzheimer: posicionamiento y recomendaciones de uso del Grupo de Estudio de Conducta y Demencias de la Sociedad Española de Neurología

Resumen
Introducción: El desarrollo de biomarcadores en sangre para detectar la enfermedad de Alzheimer (EA) representa uno de los avances recientes más significativos y algunos ya están disponibles para la práctica clínica. Por ello, el Grupo de Estudio de Conducta y Demencias de la Sociedad Española de Neurología ha formado un grupo de trabajo para revisar su estado actual y elaborar recomendaciones de consenso para su implementación clínica.
Desarrollo: Este documento fue elaborado por neurólogos/as del Grupo de Estudio de Conducta y Demencias de la Sociedad Española de Neurología en dos fases. Primero, un grupo coordinador definió las líneas básicas del documento, acordó recomendaciones iniciales basadas en una revisión bibliográfica y redactó un borrador. Posteriormente, la propuesta fue revisada por todo el grupo de trabajo, se consideraron todos los comentarios y el grupo coordinador ajustó las recomendaciones hasta lograr un acuerdo entre los participantes.
Conclusiones: El documento de consenso subraya la importancia del diagnóstico temprano de la EA. Recomienda interpretar los biomarcadores en sangre en el contexto clínico del paciente, no de forma aislada. Las unidades especializadas pueden empezar a emplearlos, pero esto debe acompañarse de investigación continua. Se requieren más datos para su uso en neurología general y atención primaria. No se recomienda su uso en personas asintomáticas, en cribados poblacionales o como pruebas directas al consumidor. Los sistemas públicos de salud deben facilitar su implementación, mediante la correspondiente financiación, para garantizar un acceso equitativo. Este documento debe entenderse como un marco inicial sujeto a actualizaciones periódicas según surjan nuevos datos.

Introduction

The development of blood biomarkers for the detection of Alzheimer disease (AD) is one of the most significant advances in recent years. Analytical and clinical studies have validated multiple blood biomarkers (Table 1)[1—12]; many of these have been used in research and clinical trials, and some are now available commercially. In the light of the opportunity and the challenge presented by these new techniques, the Spanish Society of Neurology's Behavioural Neurology and Dementia Study Group developed this positioning document as an initial framework for the use of blood biomarkers in clinical practice; it will be updated as new data become available.

Approximately 900 000 people in Spain are affected by dementia, with AD being the most frequent cause.[13]

Table 1 Main blood biomarkers of Alzheimer disease.

Blood biomarker	Method	References
Markers of amyloid pathology		
$A\beta_{42}$ or $A\beta_{42/40}$ ratio	Mass spectrometry, immunoassays	3,22–25
Markers of tau phosphorylation/secretion and/or tau pathology		
p-tau p-tau subtypes: p-tau181, p-tau217, p-tau231	Mass spectrometry, immunoassays	2,5,6,8–10,26,27
Markers of neuronal damage and/or neurodegeneration		
NfL	Immunoassay	12,28
Markers of astrocyte reactivity		
GFAP	Immunoassay	11,29–31

Aβ: beta amyloid; GFAP: glial fibrillary acidic protein; NfL: neurofilament light chain; p-tau: phosphorylated tau.

Thanks to progressive implementation of biomarkers, we are now able to perform a biological diagnosis, detecting the underlying pathology (β amyloid [Aβ] and tau protein deposition).[14] Although the reference techniques, such as cerebrospinal fluid (CSF) analysis and positron emission tomography (PET) with Aβ tracers, are safe and reliable, access to them is hindered by their limited availability, invasiveness, and costliness. Blood biomarkers represent a valuable alternative, as they are minimally invasive, inexpensive, and scalable, promoting equity of access to these advances.

Aetiological diagnosis of AD has considerable benefits for patients and their families.[15] It is currently possible to establish an accurate, early diagnosis (before the dementia phase), enabling early onset of specific treatments, access to social and economic support, and appropriate planning for the future. Furthermore, in the light of the potential availability in the future of disease-modifying therapies,[16–18] such as anti-amyloid drugs, biological confirmation of AD through the use of biomarkers is essential to the effective implementation of such treatments.[19] Blood biomarkers were recently included in the new diagnostic criteria for AD.[20]

This article briefly reviews the current status of blood biomarkers, establishes the minimum requirements for their implementation in clinical practice, explores possible contexts for their use, and addresses relevant ethical considerations. Finally, we will present some general recommendations for the clinical implementation of these biomarkers. Although it is important to note that biomarkers can be used for other purposes (Supplementary material, Table 1), the focus of the present study is on their potential use in patient diagnosis.

Current status of blood biomarkers for Alzheimer disease

The development of new, highly sensitive analytic techniques has enabled the detection of CNS proteins in the blood at femtomolar concentrations. These techniques include single molecular array (Simoa) and electrochemiluminescence (ECL) assays. In addition to immunoassays, methods using immunoprecipitation coupled to mass spectrometry have shown a comparable diagnostic yield to CSF analysis and amyloid PET studies, the current reference techniques.[21]

The main blood biomarkers of AD can be classified as biomarkers of amyloid pathology ($A\beta_{42}$ and $A\beta_{42/40}$ ratio), tau pathology (p-tau181, p-tau217, and p-tau231), astrocyte reactivity (glial fibrillary acidic protein [GFAP]), and neuronal/axonal damage (neurofilament light chain [NfL]) (Table 1).[2,3,5,6,8–12,22–31]

Blood Aβ peptides

Numerous techniques are currently available for determining blood Aβ peptide levels, including mass spectrometry[3,22,23] and automated immunoassays.[24,25] Several studies have shown that blood $A\beta_{42}$ levels, and more specifically the $A\beta_{42/40}$ ratio, are inversely correlated with amyloid PET results, and are able to differentiate between patients with and without amyloid deposition. In a study comparing 8 different blood $A\beta_{42/40}$ assays, with CSF analysis and amyloid PET as the reference techniques, receiver operating characteristic (ROC) curve analysis revealed a greater area under the curve (AUC) for mass spectrometry techniques than those obtained with various immunoassays.[32] The discriminative capacity of some immunoassays improves when *APOE* ε4 genotype is taken into account.[23,33]

Despite the promising results of these biomarkers, some limitations should be taken into account. The difference in blood Aβ levels between individuals with positive and with negative amyloid PET results is modest, with a reduction of 8%–15%. This reduction is significantly smaller than that observed in CSF results, which ranges from 40% to 60%.[34,35] This is particularly relevant when assessing the technical robustness of an assay. For consistent, clinically valuable classification of patients, the percentage change in a biomarker must be greater than the total measurement error. Furthermore, blood Aβ measurement is more sensitive than other biomarkers to variations in pre-measurement conditions and to the effects of certain drugs.[36,37] In addition, the correlation between the different assays is weak, suggesting that the different tests probably detect different

forms of Aβ. Finally, increased blood-brain barrier permeability may modify the correlation between blood and CSF Aβ peptide determinations.[38]

Phosphorylated tau protein

Phosphorylated tau (p-tau) is the most promising blood biomarker in AD. Phosphorylated tau proteins in the blood represent a reduced fraction (approximately 5%) compared to the levels present in the CSF, which constituted a severe obstacle to their quantification prior to the arrival of ultrasensitive techniques. For many years, assays developed for CSF analysis, specifically targeting the middle region of the tau protein, were also used for blood-based measurements. However, the N-terminal region is now known to be the most abundant tau fragment in the blood. The development of assays targeting this N-terminal region has enabled more precise measurement of these proteins in the blood.[26,39]

Measurement of plasma tau phosphorylated at threonine 181 (T181; p-tau181),[2,5,6,26] threonine 217 (T217; p-tau217),[8,27] or threonine 231 (T231; p-tau231)[9,10] presents high diagnostic yield for differentiating AD from other neurodegenerative diseases, even in the mild cognitive impairment phase. These results have been validated in post mortem neuropathological studies, the gold standard test.[40] In some cases, the diagnostic yield of plasma p-tau biomarkers is comparable or only marginally inferior to that of CSF or amyloid PET biomarkers.[7,21,41] Furthermore, as with blood Aβ, mass spectrometry and immunoassay techniques are available to detect p-tau, with both approaches showing good diagnostic yield.[41] The first blood biomarkers targeted T181 phosphorylation, as was the case with CSF assays, with excellent results.[2,5,6,26] Subsequent studies have reported that assays targeting T217 phosphorylation generally present greater diagnostic accuracy.[4,8,27] Furthermore, p-tau217 levels increase in line with disease progression,[42] with some reports indicating that this biomarker may be of some value for assessing the response to anti-amyloid treatment; however, more data are needed to confirm this.[43] Some p-tau217 assays are now available commercially, and are being tested in daily clinical practice.[4,7,41]

A special case is that of p-tau231, whose levels increase very early in cognitively healthy individuals with subtle changes in CSF Aβ levels, even before clear signs of amyloid deposition are detectable with amyloid PET.[9,10,42,44] Therefore, p-tau231 is a biomarker that could be used to detect individuals at high risk of AD-associated cognitive impairment in order to start preventive measures in this group. It should be noted that p-tau181, p-tau217, and p-tau231 levels increase before evidence of tau deposition becomes apparent on tau PET imaging, suggesting that these biomarkers reflect changes in soluble tau levels in response to amyloid pathology. In contrast, new biomarkers (such as NTA-tau,[45] p-tau205,[46] and p-tau212[47]) have recently been developed whose levels increase later during disease progression, reflecting deposition of insoluble tau protein. Finally, we should underscore that the total tau (t-tau) level in the blood presents poor discriminative capacity compared to p-tau, probably due to the existence of a peripheral source of the protein. To avoid this problem, a brain-derived tau (Bd-tau) assay has been developed; this biomarker is specific to the central nervous system, and may be considered a marker of neurodegeneration.[48]

Neurofilament light chain

NfL level is an indicator of neuronal and axonal damage, and increases to a greater or lesser extent in the majority of neurological diseases, both in the CSF and in the blood. Blood NfL levels are particularly elevated in prion diseases, frontotemporal dementia, amyotrophic lateral sclerosis, and 4-repeat tauopathies.[12] Blood NfL levels correlate very well with CSF levels, unlike total tau levels, which are less robust and are subject to various confounding factors due to peripheral expression of the protein. NfL is not a specific marker of AD, but does indicate the level of degeneration occurring in the disease. In fact, NfL is considered as part of the variable ''N'' (neurodegeneration) in the A-T-N classification of AD.[49] Currently, blood NfL levels are also measured in such other neurological diseases as multiple sclerosis, as a biomarker of treatment response.[50] As NfL levels increase in line with age, different cut-off points should be applied as a function of patient age.[51,52]

GFAP

GFAP is a biomarker of astrocyte reactivity; its levels begin to increase in preclinical stages of AD, and continue to increase in symptomatic phases.[11,29—31] Surprisingly, and unlike other biomarkers, the increase in GFAP level is greater in the blood than in the CSF. Furthermore, plasma GFAP level has a greater capacity to detect AD than CSF GFAP level.[11] In any case, GFAP is not specific to AD, and increases in other neurodegenerative diseases, such as Creutzfeldt-Jakob disease, Lewy body dementia, and some forms of frontotemporal dementia.[53,54] Despite this, recent studies of clinicopathological cohorts show that serum GFAP determination is useful for differentiating AD from other dementias, even in advanced phases.[55]

Minimum requirements for the use of blood biomarkers in clinical practice

To ensure adequate implementation of blood biomarkers in clinical practice, it is essential that certain minimum requirements are established, for both technical and clinical aspects. It is important that these requirements be established in advance, in the light of the continuing development of new assays. Funding by the National Health System is an important requirement for their use in clinical practice, and the technique must be validated locally in the majority of cases.

Technical requirements

The first step in evaluating a biomarker is its analytical validation, in which an assay is shown to be reliable for its intended use. Firstly, the assay must be shown to specifically measure the analyte in question. Such other parameters as precision, sensitivity, dynamic range, and robustness must

also be assessed. Furthermore, it is necessary to identify any pre-analytical factors associated with sample extraction, processing, and storage that may affect measurement of the biomarker. International recommendations now exist to minimise the impact of these factors on results,[56] and standardised, evidence-based working procedures have been developed. Although the majority of biomarkers can reliably be measured in serum, most studies have used plasma (specifically, EDTA plasma); therefore, determination in plasma is the most recommended approach.

As has previously been shown with CSF analysis, the use of automated assays helps to ensure the reproducibility of results. It is also essential for manufacturers to ensure the consistency of their assay kits between batches. Such bodies as the International Federation of Clinical Chemistry and Laboratory Medicine and the Joint Committee for Traceability in Laboratory Medicine are coordinating to develop certified reference materials and methods to enable standardisation of assays.[57] This standardisation will be essential to the comparison of results between studies, and for establishing global limits and cut-off points. Until that is achieved, however, blood biomarker results must be interpreted and verified locally, as they will be specific to each individual assay and laboratory.[58] Furthermore, the performance of the assays must be followed up to ensure the validity of cut-off points. Some quality control programmes, such as the Alzheimer's Association QC Program,[59] have already included the blood biomarkers showing the greatest potential with a view to monitoring the analytical variability of these markers between laboratories and over time.

Clinical requirements

Once the technical validity of blood biomarkers is established, they must be validated clinically through studies of cohorts representative of the population where they are to be implemented. Studies comparing cases (patients with AD) and controls are insufficient. Studies must reflect daily clinical practice, including groups of symptomatic patients with different levels of cognitive impairment, clinical presentations, and comorbidities, in whom AD is included in the differential diagnosis. Blood biomarkers must show good concordance with the gold standard test (neuropathology study) or, where this is not available, the existing methods approved for healthcare use (CSF analysis and amyloid PET).[58]

Clinical robustness also involves the ability of blood biomarkers to provide consistent, reliable results in different clinical contexts and populations. Assessment of robustness must take into account variability associated with age, sex and gender, ethnicity, body mass index, lifestyle factors, genetic variations, certain comorbidities (especially those affecting kidney function), and the use of drugs with a known impact on the results of certain blood biomarkers.[57,58,60] It is essential to understand the factors associated with heterogeneity of measurements and affecting their interpretation; this is particularly significant when defining normal ranges. Typically, biomarkers are initially studied in research cohorts that are not always representative of the population in which the biomarker will be implemented, which tends to be much more heterogeneous. Therefore, studies with more diverse populations are needed.

Assays are usually evaluated by calculating the AUC in a ROC curve analysis, in addition to sensitivity and specificity (a glossary of terms is included in the Supplementary material, Table 2). The published results show great variety, even in assays measuring the same analyte, as there may be differences between platforms. It should be noted that the CSF assays approved by the United States Food and Drug Administration (FDA) present sensitivity and specificity values of 88%—92% and 84%—93%, respectively, with amyloid PET as the reference test.[61,62] It would be reasonable to require blood biomarkers to present a similar diagnostic yield.

Biomarker development

The development of diagnostic biomarkers occurs in 5 phases.[63—65] The initial exploratory studies (phase 1) are followed by the clinical development and validation of assays (phase 2). In phase 3, biomarkers are studied in retrospective longitudinal cohorts to define criteria for negativity and positivity. The last phases are the prospective validation of biomarkers in everyday clinical practice (phase 4) and analysis of their clinical implementation and impact on decision-making (phase 5). For some blood biomarkers (Aβ, p-tau), phases 1—3 are largely complete, with studies underway to enable completion of phases 4 and 5.[64,65]

Use contexts

Current care pathway of patients with cognitive symptoms. Unmet needs

Though there are differences between centres and autonomous regions, the care pathway of patients with cognitive symptoms generally begins in primary care, with the patient or their family expressing concern about cognitive and/or behavioural problems. In this phase, early cognitive screening tests are performed and studies are conducted to identify potentially reversible causes of cognitive impairment. Patients are referred to specialist care if this is considered necessary. Specialist management includes neuropsychological assessment, neuroimaging studies, and, when indicated and feasible, CSF analysis, PET imaging with different tracers, and/or genetic studies, with a view to achieving an aetiological diagnosis. It should be noted that despite the availability of these tests in all autonomous regions, their use varies considerably, with rates ranging from 20% to 90% of eligible patients, according to a survey conducted by the Spanish Society of Neurology.[66] This disparity, together with the scarcity of neurologists specialising in cognitive impairment, results in significant diagnostic delays and, consequently, suboptimal care. In the light of the potential introduction of disease-modifying therapies, blood biomarkers may play a decisive role in increasing the percentage of patients with an aetiological diagno-

sis, helping make access to these novel treatments more equitable.

We should also discuss the possible use contexts of blood biomarkers. The clinical implementation of a biomarker must evaluate positive and negative predictive values, i.e., the likelihood that a patient with a positive or negative result, respectively, has AD or not (see the glossary; Supplementary material, Table 2). These parameters depend not only on the characteristics of the assay, but also on the prevalence of the disease in question, which will differ between specialised units, general neurology consultations, primary care populations, and the general public.

Use at specialised units

Specialised units attend a population with high prevalence of AD, in whom blood biomarkers have already been studied, with very promising results. Specifically, such blood biomarkers as p-tau217 (measured by mass spectrometry) have even been found to be equivalent to FDA-approved CSF studies in classifying amyloid PET status.[21] However, mass spectrometry techniques are not currently available at the majority of centres, and probably will not become available in the medium term. Some p-tau217 immunoassays are now available and have shown excellent performance in detecting AD, including in Spanish cohorts.[4,7] As a result, these assays have been proposed as a replacement for CSF analysis or amyloid PET imaging. Nonetheless, these data are from retrospective studies of clinical research cohorts; therefore, further research is needed to confirm the findings in prospective studies with pre-established cut-off points and more heterogeneous patient populations.

In the light of these considerations, and despite the promising results of blood biomarkers, our study group proposes that they be implemented progressively, by phases, beginning with specialised units. We cannot currently recommend that they fully replace CSF analysis or amyloid PET. In an initial phase, blood biomarkers would complement the reference tests. In a subsequent phase, after accumulation of sufficient evidence on the use of blood biomarkers in daily clinical practice, they may be considered as a replacement for CSF analysis and amyloid PET in certain specific contexts.

Several different approaches, using different cut-off points, would be acceptable for this initial phase of implementation. A first approach would be the use of 2 cut-off points, calculated to ensure high specificity (90%, 95%, or 97.5%) and high sensitivity (90%, 95%, or 97.5%), respectively.[67] Thus, patients would be classified into 3 categories according to the level of the biomarker: an upper category, with a high positive predictive value (minimising false positives), an intermediate category, and a lower category with high negative predictive value (minimising false negatives). CSF analysis or amyloid PET studies would only be necessary in the intermediate category; this would lead to considerable cost savings. If CSF analysis or amyloid PET cannot be performed (due to contraindications or lack of availability), these patients should be reassessed over time; repeated measurement of the blood biomarker should also be considered in these reassessments.

Alternatively, a single cut-off point could be used, but in this case results must always be interpreted with caution, accounting for the pre-test probability of AD. On the one hand, a cut-off point with high sensitivity could be used in populations with low pre-test probability of AD (e.g., younger patients or those with atypical presentations), with the exclusive aim of ruling out the disease. In this context, negative results would constitute reasonable grounds to rule out the presence of AD. In the event of positive results, further studies would be justified. On the other hand, a cut-off point with high specificity would be used in populations with high pre-test probability of AD (e.g., older patients or those with typical presentations), with a view to confirming the diagnosis. In this second context, positive results would confirm the clinical suspicion of AD, and treatment could be started without further delay. Negative results would not rule out the diagnosis of AD, and further study would be required; this may include CSF analysis or amyloid PET, if these studies were considered necessary. This second strategy may also be helpful in patients for whom lumbar puncture or amyloid PET are contraindicated or cannot be performed.

Given their availability and accumulated experience, we consider specialised units to be the ideal setting for the initial implementation of these biomarkers in clinical practice. The decision to use one or 2 cut-off points would be made by each centre.

Use at general neurology consultations

In Spain, patients with cognitive impairment are frequently assessed at general neurology consultations. Currently, there are considerable disparities between centres both in the level of clinical experience and in the use of diagnostic biomarkers, access to cognitive testing, and AD prevalence. Unquestionably, we must prioritise the development of specialised units across Spain, incorporating such new advances as blood biomarkers of AD.

In order to use these blood biomarkers at general neurology consultations, a series of conditions must be met: understanding on the part of the medical team of how results are interpreted and the potential confounding factors; knowledge of how to correctly communicate the results; the existence at the laboratory of a standardised working procedure; and the validation of cut-off points. The majority of studies of blood biomarkers have been conducted at specialised units; therefore, this knowledge must still be expanded to non-specialised consultations.

In the future, and following the approaches described above, a result with high negative predictive value may be sufficient for ruling out AD at general neurology consultations. It should be noted that ruling out AD does not imply that other neurological diseases or other causes of cognitive impairment are also ruled out; in many cases, diagnostic work-up of the patient must continue. Similarly, results with high positive predictive value could confirm AD, facilitating onset of the indicated treatment. However, we consider

Table 2 Recommendations of the Behavioural Neurology and Dementia study group.

1. Blood biomarker studies for AD diagnosis should be promoted. Early aetiological diagnosis of AD is essential to the early onset of appropriate treatment, and to provide patients and their families with the best possible information and care.
2. Prior to their implementation in clinical practice, blood biomarkers must show strong concordance with current reference studies, i.e., CSF analysis and amyloid PET, or neuropathological findings. Study cohorts must present comparable characteristics to those of the population in which these biomarkers will be used.
3. Blood biomarkers must always be interpreted within their clinical context, after appropriate history-taking and neurological and cognitive examination, after ruling out reversible causes of cognitive impairment. They must not be used in isolation.
4. Blood biomarkers of amyloid and/or tau pathology (e.g., $A\beta_{42}$, $A\beta_{42/40}$, or various forms of p-tau) are the most appropriate measures for detecting Alzheimer-type pathology. Within this group, p-tau217 shows the most promising results and, if measured with automated immunoassays, is the most feasible for use in clinical practice and the most easily scalable.
5. Blood biomarkers should be progressively incorporated into clinical practice; we cannot currently recommend that they replace CSF analysis or amyloid PET, which continue to be the reference tests.
6. The available evidence is sufficient for specialised units to begin using blood biomarkers without further delay. Nonetheless, this implementation must be supported by constant research and quality control assessing local cut-off points, use of these tests in clinical practice, and their impact on patients, their families, and the healthcare system.
7. More data, training, and appropriate infrastructure are needed for blood biomarker determination to be implemented in general neurology consultations and primary care.
8. We currently advise against the use of blood biomarkers in asymptomatic individuals and for population screening, unless used exclusively in research contexts.
9. We advise against the use of blood biomarkers as a direct-to-consumer test. Biomarker tests must always be prescribed, interpreted, and reported to patients by a suitably trained healthcare professional.
10. Public healthcare systems should take a leading and guiding role in the implementation of blood biomarkers and other advances in AD, through the inclusion of these studies in the portfolio of healthcare services, thus ensuring equitable access.

Aβ: beta amyloid; AD: Alzheimer disease; CSF: cerebrospinal fluid; p-tau: phosphorylated tau; PET: positron emission tomography.

that general consultations should have access to aetiological studies and the capacity to refer patients to a specialised unit. The latter point is particularly crucial in the light of the potential future availability of disease-modifying therapies, for which AD diagnosis should be confirmed with the current reference tests. In conclusion, we recommend that the use of blood biomarkers at general neurology consultations be restricted to situations of close collaboration with specialised reference centres for the progressive implementation of these techniques.

Use in primary care

The prevalence of AD and other dementias in primary care settings is lower than in specialised units or general neurology consultations; therefore, biomarkers would have a greater negative predictive value. While negative results may rule out AD, patients with positive results should be referred to specialised units for further study and confirmation of the diagnosis of AD. This would streamline the clinical management of these patients, with priority referral of patients with high likelihood of AD; this would have significant repercussions in settings with limited specialised resources. In a potential context in which disease-modifying therapies are available, this approach would also accelerate the detection of potentially eligible patients and, no less important, promote equity of access to these drugs. Once more, it should be noted that a negative result from a blood biomarker study does not rule out diseases other than AD; therefore, work-up should be continued, with referral to specialised units if necessary.

However, we believe the available data are currently insufficient to recommend the use of blood biomarkers in primary care settings. More real-world clinical experience from these settings is needed, as well as clinical guidelines and specific training for primary care professionals.

Studies in the general and asymptomatic population

Although AD is a common disease, its prevalence in the general public is obviously lower than that observed at medical consultations. Population screening requires highly sensitive and specific, inexpensive, and widely available tests; above all, there must be a disease-modifying therapy that may be used in patients with positive results. We must also consider the impact of a positive result on a patient's life and psychological status. Currently, these requirements are not met; therefore, we do not recommend the use of blood biomarkers for population screening or in asymptomatic individuals, except as part of research studies.

Nonetheless, this is a relevant subject for debate. In the light of the results of recent studies with anti-amyloid drugs, which demonstrate that disease stage modulates treatment response, the future use of these drugs in preclinical phases seems plausible. This would require the nationwide availability of infrastructure to screen for, identify, and treat a high number of individuals at high risk of developing AD.

We should also mention the demonstrated effectiveness of some multimodal non-pharmacological interventions in preventing dementia.[68]

Clinical trials: recruitment and monitoring of treatment response

A relevant challenge that limits and slows recruitment to clinical trials of disease-modifying drugs for AD is the high rate of screening failure due to the lack of cerebral amyloid deposition (30%—40% in the prodromal and mild dementia phases and 80%—90% in the preclinical phase).[69] The majority of clinical trials of AD currently require aetiological confirmation with CSF analysis and/or amyloid PET. Blood biomarkers may significantly reduce rates of screening failure and the number of lumbar punctures and PET scans needed; this would reduce costs and delays in the approval of new treatments.

Another critical consideration is the monitoring of treatment response. Due to their inherent characteristics, blood biomarkers are ideal for repeated measures; some of them, such as p-tau217, have already been used as pharmacodynamic biomarkers in clinical trials.[16,43] However, further data are needed before p-tau217 can be used as a surrogate marker of amyloid PET for monitoring amyloid load in clinical trials.

Ethical considerations. Informing patients and their families

When using blood biomarkers, like any other test under development, it is essential that patients and their families be made aware of the limitations of the test and its interpretation, both before and after it is conducted. Given the potential relevance of the results, it is fundamental that patients be allowed to decide independently whether they wish to undergo testing. When communicating both with patients undergoing the test and with non-specialist media, the use of appropriate language is crucial in ensuring that concepts are correctly understood. It is important to consider that the term ''early diagnosis'' is used differently by experts in this context than how it is often interpreted by the general public. We must endeavour to make it clear at all levels that this term refers to patients who are already experiencing symptoms, and not to the use of blood biomarkers to predict the future risk of developing AD in an asymptomatic individual; these biomarkers are not currently recommended for this indication. Another relevant misunderstanding is in the interpretation of results; it must be made clear that these studies do not currently provide information on disease stage or prognosis. Though it is not the case in Spain, some companies in such other countries as the United States offer blood biomarkers studies on a direct-to-consumer basis. Currently, we consider this practice to be unacceptable in our setting, as it falls outside their recommended use, both in terms of patient profile (presence/absence of symptoms or potential confounding factors are not taken into account) and use context (the test is not prescribed or interpreted by experts).

Future perspectives and recommendations

Some blood biomarkers have now passed phases 1—3 of development, and have shown excellent diagnostic yield in retrospective cohorts. Next, we must start phases 4 and 5, in which we must evaluate their use in real patients in everyday clinical practice, and establish the impact on patients and their families. In this regard, we consider the available evidence to be sufficient for specialised centres to begin using blood biomarkers without further delay, and assessing their performance and impact (Table 2). As this evidence is gathered from the Spanish population, we believe that it will be possible to expand the use of blood biomarkers to general neurology consultations, in collaboration with specialised units, within a reasonable timeframe. However, further study is needed before these tests can be implemented in primary care or for population screening.

Although clinical implementation may become a reality in the short to medium term, considerable outstanding challenges remain. Firstly, the determination and interpretation of cut-off points are critical. Secondly, it is essential to understand all the individual factors that may influence the measurement and the diagnostic yield of biomarkers. Future studies should account for the diversity of our patient populations. Furthermore, we must consider the presence of multiple diseases when interpreting the results, as neuropathological studies have shown that the majority of patients with AD also present other co-pathologies. We also lack reliable blood biomarkers for many other neurodegenerative diseases. While this article focuses on the diagnostic value of blood biomarkers, a biomarker may also provide prognostic and/or predictive information; this should be addressed by longitudinal studies (Supplementary material, Table 1). Finally, it is essential to remember the obvious: a biomarker must always be considered within the clinical context, and must never be a replacement for clinical judgement.

Blood biomarkers present clear advantages over CSF analysis and amyloid PET: they are perceived by patients and healthcare professionals to be more acceptable and safer (although lumbar puncture and PET scans are both thoroughly safe); they require fewer specialised staff, making them more accessible to the population; they have no contraindications; and they can facilitate diagnosis in less represented populations, promoting equity of access to healthcare. With a view to guaranteeing this equity, we believe that public healthcare systems must play a key role in ensuring that these new advances are made available to the entire population. To reduce dependence on external aid, funding by the National Health System is an important requirement for their use in clinical practice (Table 2).

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CRediT authorship contribution statement

All authors contributed substantially to study conception, drafting of the manuscript, and revision of the intellectual content, and approved the final version of the article.

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Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.nrleng.2025.07.004.

Declaration of competing interest

AGM has given lectures at conferences sponsored by TEVA, Almirall, and Lilly, and has received funding from Instituto de Salud Carlos III (ISCIII), the European Union (ESF+), and the European Regional Development Fund in accordance with O.A., M.P. of 13 December 2023, through a Juan Rodes fellowship (JR23/00005).

AV has received personal payments from Schwabe, Alter, KRKA, Kern Pharma, Esteve, and Neuraxpharm for participating in educational events and from Eisai for participating in advisory committees.

CA has received a research grant from the Susan and Charles Berhoff Foundation. She has given lectures at conferences sponsored by Hoffman-La Roche Ltd and Nutricia, with payment made to the institution (Ace Alzheimer Center Barcelona). She has received funding to attend international conferences from Biogen Inc and Nutricia, with payment made to the institution (Ace Alzheimer Center Barcelona). She has received personal payments from lectures at symposia sponsored by F. Hoffman-La Roche Ltd, Nutricia, Schwabe Farma Ibérica S.A.U., and Zambon. She is a member of the board of directors of the Lewy Body Dementia Association and ad honorem member of the scientific committee of Lewy Body España.

GAF has given lectures at training activities sponsored by GE HealthCare and Fujirebio. He has participated in an advisory committee for GE HealthCare.

MS-C has given lectures at conferences sponsored by Almirall, Eli Lilly, Novo Nordisk, Roche Diagnostics, and Roche Farma. He has consulted and participated in advisory committees for Eli Lilly, Grifols, and Roche Diagnostics. He has been granted project funding and is a clinical trial researcher for Roche Diagnostics International Ltd. He has received support in kind for research from ADx Neurosciences, Alamar Biosciences, Avid Radiopharmaceuticals, Eli Lilly, Fujirebio, Janssen Research & Development, and Roche Diagnostics. All payments were made to the institution (BBRC).

NR-E has given lectures at conferences sponsored by Almirall and Roche Farma and is a researcher in an observational study funded by Roche Farma.

EM-R has received personal payments for lectures sponsored by KRKA Farmacéutica S.L.

RS-V has received personal payments from Roche Diagnostics, Lilly, and Neuraxpharm for participating in educational events, and from Eli Lilly, Pfizer, and Wave Pharmaceuticals for participating in advisory committees.

The remaining authors have no conflicts of interest to declare.

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