14th COGNITIVE DAY

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From Brain Ageing to Treatment: Risk, Biomarkers, and Memory Clinics

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Preface

PREFACE

Dear colleagues,
It is our great pleasure to welcome you to **the 14th Cognitive Day and to this Book of Abstracts.**

Cognitive Day has become a well-established annual scientific meeting, bringing together neurologists, psychiatrists, and other members of multidisciplinary teams dedicated to the care and research of cognitive disorders. With strong and growing international participation, the meeting continues to serve as an important platform for the exchange of knowledge, experience, and ideas. It is jointly organized by the Centre for Cognitive Impairments, Department of Neurology, University Medical Centre Ljubljana, and the Slovenian Medical Association.

The 14th Cognitive Day is dedicated to key contemporary challenges in the field, with a focus on brain ageing, early diagnosis, and emerging disease-modifying therapies for Alzheimer's disease. Particular attention will also be given to the evolving organization and readiness of memory clinics in response to these advances. The meeting is held under the subtitle. **"From Brain Ageing to Treatment: Risk, Biomarkers, and Memory Clinics"** The scientific program features distinguished international and Slovenian experts, and we hope it will stimulate insightful discussion and foster further interdisciplinary collaboration.

We warmly welcome all participants and readers of this Book of Abstracts and wish you a productive and inspiring meeting.

On behalf of the Scientific and Organising Committee

Associate Professor Milica GREGORIČ KRAMBERGER, MD, PhD

Program

08:30 - 09:00 **Registration**

09:00 **Welcome and introduction**
Milica G. KRAMBERGER, Ljubljana, Slovenia

BRAIN AGEING

09:05 **Vascular and Alzheimer's interplay in cognitive decline: Insights from population studies**
Anna MARSEGLIA, Stockholm, Sweden

09:35 **A neuroimaging indicator of biological brain age in ageing and neurodegenerative disorders**
Eric WESTMAN, Stockholm, Sweden

10:05 **Cerebral Amyloid Angiopathy in Memory Clinic Patients: A Radiological Perspective**
Ernest Privšek, Ljubljana, Slovenia

10:20 - 10:30 **Discussion**

RISK FACTORS

10:30 **Nutrition as part of a strategy for dementia prevention**
Anja MRHAR, Ljubljana, Slovenia

10:50 - 11:00 **Discussion**

11:00 - 11:20 **Coffee Break**

11:00- 11:20 ***BIOMARKERS***

11:20 **PRO&CON: Blood-based biomarkers should be used for early screening of Alzheimer's disease**
Andreja EMERŠIČ, Ljubljana, Slovenia
Fernando GONZALEZ-ORTIZ, Gothenburg, Sweden
- 5 min Introduction and pre-debate voting: moderator Milica G. Kramberger
- 15 min Pro: Andreja Emeršič, Laboratory for CSF diagnostics, University Medical Centre Ljubljana
- 15 min Contra: Fernando Gonzalez-Ortiz, University of Gothenburg, Sahlgrenska University Hospital
- 10 min Discussion, rebuttals, and post-debate voting

12:05 **Amyloid imaging in clinical practice**
Tomaž RUS, Ljubljana, Slovenia

12:20 **Implementation of Amyloid-Targeting Therapies (ATTs) in Cognitive Clinics: Lessons Learned After 2 Years of Real World Experience**
Noa BREGMAN, Tel Aviv, Israel

12:50 - 13:00 **Discussion**

13:00 - 14:00 **LUNCH**

MEMORY CLINIC READINESS

14:00 **Estimates of current capacity for diagnosing and implementation of new treatment of Alzheimer's disease in Slovenia**
Eva ŽUPANIČ, Ljubljana, Slovenia

14:20 **From Science to Clinical Practice: Preparing Memory Clinics for the Era of Disease-Modifying Alzheimer's Therapies**
Sebastiaan ENGELBORGHS, Brussels, Belgium

14:40 - 15:10 **Round table discussion**
moderator Zvezdan P IRTOŠEK,
Sebastiaan ENGELBORGHS, Marina BOBAN,
Eva ŽUPANIČ, Polona RUS PRELOG

15:10 **Closing remarks**

Vascular and Alzheimer's interplay in cognitive decline: Insights from population studies

Anna MARSEGLIA, PhD

Alzheimer's disease and cerebrovascular disease are among the leading causes of cognitive impairment and dementia in older adults, and frequently co-occur in the ageing brain. Multimodal data integrating fluid and imaging biomarkers with clinical and behavioral data, provide a comprehensive framework for disentangling how vascular and Alzheimer's disease pathologies additively and synergistically influence brain structure, as well as downstream cognitive and behavioural outcomes. The goal of this talk is to explore how cerebrovascular disease interacts with Alzheimer's pathology to influence cognitive outcomes, focusing on sex-specific differences. Using updated VASCOG-2-WSO criteria, we analyzed large population-based cohorts with multimodal data—brain MRI, fluid biomarkers, health-related, clinical and cognitive assessments—to classify vascular cognitive impairment and dementia (VCID) and identify key determinants. Findings highlight the role of cardiometabolic comorbidities, lipid metabolism, and lifestyle factors in VCI progression, with notable differences between men and women. We will also discuss how Alzheimer's co-pathology modifies these associations, offering insights into personalized strategies for dementia prevention and intervention.

A neuroimaging indicator of biological brain age in ageing and neurodegenerative disorders

Eric WESTMAN, PhD

Background

Predicted brain age (PBA) is an estimate of the biological brain age (BA), different from chronological age (CA). It has been shown that the brain age gap (BAG), the difference between PBA and CA, is a promising marker of brain health and accelerated aging. Greater BAG has been shown to be related to atrophy, cerebrovascular alterations, and worse cognition in cognitively unimpaired individuals (Marseglia et al., 2025). However, the relationship between BAG and neuroimaging markers and cognition in individuals along the Alzheimer's disease (AD) continuum is not well understood.

Methods

A brain age model was trained on structural MRI data from cognitively unimpaired individuals (CU) from six international multi-center cohorts using an in-house developed BA model (Dartora et al., 2024; Marseglia et al., 2025). The BAG was compared along the AD continuum from CU to mild cognitive impairment (MCI) to AD. Brain maps illustrating the relationship between BAG (subjects with older-looking, age-like, and younger-looking brains) and atrophy (MRI), glucose metabolism and Tau (PET) were created. Cognitive trajectories for the same groups were also calculated. Results were validated in external data sets.

Results

Predicting BA in amyloid positive subjects, we observe that a more typical AD pattern of tau pathology and reduced glucose metabolism (Figure 1A) exists in all groups, younger, age-like, and older looking brain in both MCI and AD. Atrophy on the other hand increases more in relation to BAG. The BAG also predicted cognitive decline but only in individuals with MCI (Figure 1B). Similar results were observed in validation cohorts as well as in clinical cohorts from three memory clinics across Europe.

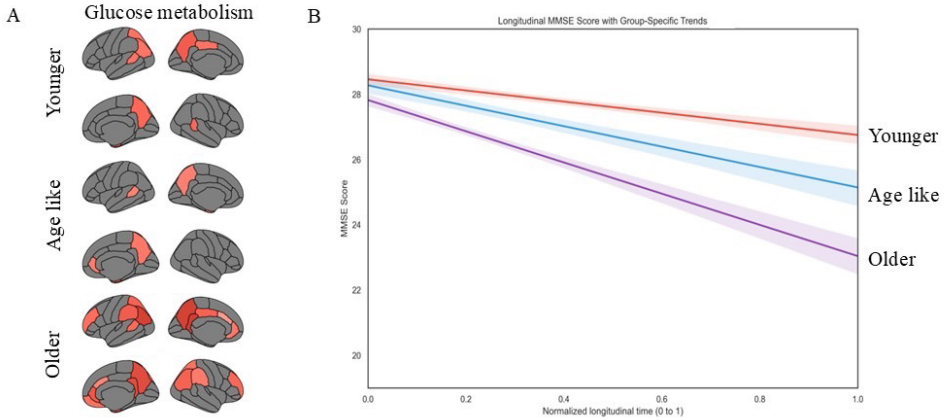

***Figure 1**: Brain age in mild cognitive impairment (MCI)*
***A)** Typical predominantly posterior glucose metabolism (PET) pattern in amyloid positive MCI individuals. Similar patterns are observed in individuals with younger, age like as well older looking brain predicted by our brain age model using MRI as input (Dartora et al., 2024). **B)** The rate of cognitive decline is significantly faster in subjects with an older looking brain compared to those with an age-like brain or younger looking brain.*

Conclusion

Our findings illustrate that BA may be independent from brain changes related to AD. The findings also show the potential use of BA for predicting future cognitive decline in individuals with MCI. The faster cognitive decline observed in MCI with an older-looking brain may be due to vascular pathology (Marseglia et al., 2025), an important co-pathology in AD lowering the threshold for cognitive impairment (Jack et al., 2024).

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Cerebral Amyloid Angiopathy in Memory Clinic Patients: A Radiological Perspective

Ernest PRIVŠEK, MD, PhD Student

CAA in the Aging Brain

Cerebral amyloid angiopathy (CAA) is a common age-related small vessel disease characterized by amyloid-β deposition in cortical and leptomeningeal vessels. Its prevalence increases with advancing age and is particularly high in populations with cognitive impairment, yet it remains underdiagnosed in vivo. In clinical practice, CAA is typically inferred through magnetic resonance imaging (MRI) using the Boston Criteria, as definitive diagnosis requires histopathological confirmation. However, MRI-based diagnosis captures predominantly advanced stages of the disease, leaving a substantial proportion of cases unrecognized during life.

Cerebral Microbleeds on MRI: Detection, Interpretation, and Diagnostic Role in CAA

MRI plays a central role in identifying imaging markers associated with CAA, including cerebral microbleeds (CMBs), cortical superficial siderosis, and intracerebral hemorrhage, as well as non-hemorrhagic features such as enlarged perivascular spaces and white matter abnormalities. Among these, CMBs are of particular importance due to their diagnostic relevance, association with vascular fragility, and emerging role in guiding treatment decisions. Nevertheless, detection and interpretation of these lesions remain challenging in routine practice, as they are influenced by imaging protocols, reader experience, and the presence of mimics. Standardized rating approaches improve reliability, but variability persists, particularly in cases with low lesion burden or complex imaging appearances.

Expanding the Spectrum: Boston Criteria 2.0

The recently updated Boston Criteria version 2.0 incorporates both hemorrhagic and non-hemorrhagic imaging markers, representing a shift toward increased sensitivity. In memory clinic populations—where mixed vascular and neurodegenerative pathology is common—this update substantially increases the proportion of patients classified as possible or probable CAA. This effect appears to be largely driven by the inclusion of non-hemorrhagic markers, particularly enlarged perivascular spaces in the centrum semiovale and multispot white matter hyperintensity patterns. While this broader definition may capture earlier or more subtle manifestations of the disease, it also raises concerns regarding reduced specificity, given the high prevalence and limited disease-specificity of these imaging features in aging and cognitively impaired populations.
Performance of CAA Criteria in Memory Clinics
Importantly, the diagnostic performance of the Boston Criteria varies considerably depending on the clinical context. While high sensitivity and specificity have been demonstrated in hemorrhagic stroke cohorts, performance is substantially lower in non-hemorrhagic or cognitively impaired populations, where overlapping pathologies are the rule rather than the exception. This discrepancy highlights a key limitation of applying uniform diagnostic criteria across fundamentally different patient groups.

CMBs as a Bridge Between Diagnosis and Therapy

CMBs illustrate the evolving role of MRI biomarkers at the intersection of diagnosis and clinical decision-making. Beyond their role in supporting a diagnosis of CAA, CMB burden has become a critical determinant of eligibility and safety for anti-amyloid therapies, as higher counts are associated with increased risk of treatment-related complications. As such, radiological assessment is no longer purely descriptive but directly informs therapeutic strategies.

Conclusion

In this context, CAA in memory clinic patients should be viewed as a heterogeneous, imaging-defined phenotype rather than a singular disease entity. Accurate interpretation requires careful integration of imaging findings with clinical context, awareness of methodological limitations, and an understanding of how evolving diagnostic frameworks influence disease classification. As disease-modifying therapies continue to emerge, the need for precise, standardized, and clinically meaningful MRI assessment will become increasingly important.

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Nutrition as Part of the Strategy for Dementia Prevention

Anja MRHAR, MS, PhD candidate

Dementia prevention is becoming a rising global public health priority in the context of rapidly ageing populations and limited availability of disease-modifying treatments (1). Current research on nutrition has yielded promising, but not yet definitive findings on how nutrients, foods, and dietary patterns may mitigate Alzheimer's disease (AD), one of the leading causes of dementia, and modify dementia onset (1,2). While AD pathological changes are necessary in the development of dementia, the presence of those alone is not sufficient to inevitably lead to clinical disease (3). This recognition has intensified interest in modifiable lifestyle factors - particularly nutrition - that may delay or prevent the onset of dementia specifically among individuals with underlying neurobiological vulnerability.

Accumulating evidence from epidemiologic and clinical studies suggests that overall diet quality, rather than individual nutrients, is relevant for brain health. The Mediterranean diet is the most extensively examined pattern—however not the only one—with respect to cognitive outcomes and risk of dementia (1). Both observational studies and randomized controlled trials have linked this and other healthy dietary patterns to better cardiovascular health (e.g., diabetes, hypertension, and cardiovascular diseases) (4), which has an important role in brain health and dementia development (5). Nevertheless, although several studies have assessed the association of adherence to dietary patterns with neuroimaging and cerebrospinal fluid AD biomarkers, to infer their relationship with dementia, to our knowledge no study has analyzed how dietary patterns may modify dementia risk across strata of neurobiological risk, including among individuals with AD pathology.

In parallel, advances in blood-based biomarkers—such as phosphorylated tau at threonine 217 (p-tau217), neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP)—now hold promise for identification of individuals at risk (3, 6). These biomarkers have been shown to predict incident dementia in community settings, often years before first symptoms and clinical dementia onset (6), and provide an opportunity to examine whether lifestyle factors such as diet remain relevant once biological vulnerability is detectable.

Our recent longitudinal study from a population-based cohort of 1865 dementia-free older adults followed for up to 15 years suggests that diet quality may indeed remain relevant even in the presence of biomarker-defined vulnerability. In this cohort, higher adherence to healthy dietary patterns—assessed using the Alternative Mediterranean Diet (AMED), Alternative Healthy Eating Index (AHEI), and reversed Empirical Dietary Inflammatory Index (rEDII)—was associated with lower dementia risk over long-term follow-up. Importantly, these associations differed according to underlying biomarker levels. rEDII, characterizing healthier diet by lower inflammatory potential, showed the most consistent inverse associations with all-cause dementia, as well as AD dementia, risk among individuals with elevated p-tau217, NfL, or GFAP levels, markers reflecting AD pathology, neuronal injury, and astrocytic activation, respectively. By contrast, other healthy dietary patterns were more strongly associated with lower dementia risk among individuals with lower biomarker levels. Absolute-risk analyses further indicated that adherence to diets with lower inflammatory potential may not only reduce relative dementia risk but also meaningfully delay dementia onset and prolong dementia-free life expectancy among individuals at elevated biological risk.

These findings support the relevance of diet quality in cognitive health and in scope of dementia mitigation. Additionally, the results further suggest that inflammation may be a key pathway linking diet to neurodegeneration and dementia progression. Pro-inflammatory dietary profiles have been previously associated with adverse brain outcomes, including cognitive decline and structural brain changes, whereas diets rich in plant-based foods, unsaturated fats, and bioactive compounds may mitigate systemic and neuroinflammatory processes (1,7). However, it should be noted that other mechanisms, such as oxidative stress, insulin resistance, lipid metabolism dysregulation, and the gut-brain axis, may also link diet with neurodegeneration and dementia (8).

Taken together, current evidence positions nutrition as an integral component of dementia prevention strategies across the disease continuum. Rather than being limited to primordial prevention in the general population, dietary interventions may also be relevant for primary

prevention among individuals at risk, with early AD pathology or broader neurobiological vulnerability. Future research should aim to confirm these associations in more diverse populations, clarify the specific dietary components driving the observed benefits, and determine how nutritional strategies can be optimally integrated into personalized and precision public health approaches for dementia prevention.

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Blood-based biomarkers should be used for early screening of Alzheimer's disease – Pro

Andreja EMERŠIČ, MPharm, PhD, EuSpLM

Introduction

After decades of symptomatic therapies, the newest monoclonal antibodies against amyloid-β (Aβ) finally promise a shift in Alzheimer's disease (AD) care. Lecanemab and donanemab have demonstrated dose-dependent clearance of Aβ plaques and delayed progression of cognitive decline in recent clinical trials.[1–3] These and upcoming disease-modifying interventions could help reduce the escalating burden AD poses on healthcare systems and wider society.[4,5] Following regulatory approvals, the anticipated implementation of anti-amyloid drugs in clinical practice will likely increase the need for biomarker-based diagnosis of AD. To accurately identify eligible patients, cerebrospinal fluid (CSF) or positron emission tomography (PET) confirmation of Aβ pathology is required. Established biomarkers alone, however, will hardly address the growing diagnostic demand in the new era of AD treatment, as they are tied to relatively invasive or costly diagnostic procedures in specialised facilities.[6–8] Remarkable progress in the field of blood-based biomarkers (BBM) of AD is well-timed and offers opportunities for simplified diagnostic workup and broader clinical application in the near future. Although current research does not support community-based screening for AD[7,8], there are many reasons to consider integrating BBM as a first-line screening tool in memory clinic settings.

Availability of accurate blood-based biomarkers

Several promising plasma biomarkers of AD have been developed that reliably reflect AD pathology in symptomatic individuals. Biomarkers associated with amyloid (A) and tau (T) pathology, neurodegeneration (N), and astrocyte activation show strong agreement with neuropathological hallmarks and with established CSF and PET biomarkers in AD patients. [9–14] In the latest systematic review and meta-analysis,[15] the pooled diagnostic sensitivity of plasma Aβ42/40 ratio and different phosphorylated tau (p-tau) assays varied from ~50% to 91% in cognitively impaired individuals in specialised care settings, whereas specificity ranged from ~62% to 97%, depending on the analyte and assay platform.[15] Positive and negative predictive values over 90% can thus be expected with the best-performing assays in memory clinic patients, given their estimated pre-test probability of Aβ pathology[16] (e.g., ~40% prevalence of Aβ positivity in individuals with mild cognitive impairment at age 65).

Higher accessibility and scalability of blood testing

BBMs can offer some of the main advantages of CSF tests (e.g., providing information on all ATN categories at the same time, enabling retrospective analysis in properly stored samples and allowing detection of subtle and real-time changes in brain pathology) but are more affordable and easier to implement than standard CSF and neuroimaging biomarkers.[6,17] Blood collection can be performed in a general laboratory setting or at a patient's bedside, without the need for highly dedicated facilities. As blood tests are more accessible and scalable, they could support broader, more equitable access to biomarker-based diagnosis or even enable widespread testing for AD in the future. [8]

Minimal invasiveness and cost-effectiveness of blood tests

Venipuncture is minimally invasive, usually well tolerated, and more acceptable to patients than lumbar puncture or PET, which tend to carry a higher risk of adverse events and may cause physical discomfort or anxiety.[18–20] Due to their lower direct costs and simpler procedures, BBM tests have already been incorporated into clinical trials to accelerate study enrolment and reduce total costs. [21,22] Similarly, a BBM test with a high negative predictive value could rule out memory clinic patients who do not yet need further testing, thereby reducing costs and enabling better resource allocation. A modelled two-cut-off approach to risk-stratify patients for Aβ positivity based on a high-performing plasma p-tau217 assay has been shown to reduce the number of confirmatory

CSF Aβ42/40 tests by >80%, offering a cost-effective strategy to detect underlying AD pathology. [23] BBM tests may prevent delays between symptom onset and referrals to confirmatory testing, facilitating early diagnosis of AD and timely interventions, which are more likely to preserve patients' independence and yield long-term savings.[24]

Importance of early diagnosis and timely interventions

With the arrival of disease-modifying therapies, early detection of cognitive impairment and underlying AD pathology has become increasingly important. Outcomes from recent trials suggest that amyloid-targeting drugs are more effective when administered early in the disease course, when pathology is present, but symptoms and neurodegeneration remain minimal.[25] In an open-label extension study, participants included at earlier biological stages showed stability or improvement over the 18-36 month period,[26] suggesting targeting AD at earlier stages could result in more meaningful effects. Similar to their CSF counterparts, BBMs may reflect changes very early in the disease process and become abnormal years before symptoms develop,[9,10,27] making them ideal for initial screening and risk-stratification to improve further diagnostic workflow.[25,28]

Guidelines and recommendations for appropriate use already exist

In response to significant advances in BBM development, blood tests have been included in the updated research framework, i.e., criteria for diagnosis and staging of AD by the Alzheimer's Association workgroup.[29] Variable diagnostic accuracies of available blood tests have prompted the Global CEO initiative on AD to recommend minimal acceptable performances of BBM tests. Rather than assessing specific assays, these recommendations present minimal performance standards that BBM tests should meet to be applied for screening (triaging) or confirmation of Aβ pathology. [30] According to the Clinical Practice Guideline on the use of BBMs in the diagnostic workup of AD[8], blood testing should not be performed before a comprehensive clinical workup. Guidelines suggest using BBM tests with ≥90% sensitivity and ≥75% specificity as a triage test in cognitively impaired individuals, and BBM with ≥90% sensitivity and specificity as a substitute for traditional CSF analysis or amyloid PET imaging.[8]

Conclusion

Current research and clinical guidelines support the careful implementation of BBMs in specialised care settings. When used as a first-line screening tool in memory clinic population, BBMs could streamline referral processes and facilitate early AD diagnosis and access to treatment.

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Plasma p-tau217 as a marker of progression heterogeneity rather than a baseline stratifier: Use and interpretation of plasma p-tau in clinical practice

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Phosphorylated tau at threonine 217 (p-tau217) has emerged as one of the most promising blood-based biomarkers for Alzheimer's disease (AD). However, despite its high diagnostic performance in multiple studies, important caveats remain regarding its use and interpretation.

In this talk, plasma p-tau217 data from different centers will be presented to address two main points.

First, plasma p-tau217 may be best understood as a dynamic marker of AD progression rather than as a fixed baseline stratifier. In two independent cohorts, we observed that among A+ individuals, the rate of progression varied substantially: some individuals remained cognitively stable despite being CSF/plasma p-tau217 positive. This suggests that CSF/plasma p-tau217 positivity is not necessarily a marker of symptomatic AD. Longitudinal changes in p-tau217, rather than a single baseline value, appear to be most informative for monitoring heterogeneity in disease progression and potential treatment response.

Second, increased plasma p-tau217 levels may be observed in both physiological and pathological conditions. For example, plasma p-tau217 was highly expressed in healthy neonatal cord blood samples from two different centers, despite the absence of amyloid deposition, neurofibrillary tangles, or neurodegeneration. This suggests that p-tau217 is not exclusively pathological or amyloid-dependent, but may also have physiological roles in axonal growth, synaptogenesis, pruning, and early neural plasticity. Consequently, fixed diagnostic thresholds may lead to false-positive interpretations, particularly in pediatric, asymptomatic, or atypical populations.

Overall, our results show that baseline CSF and plasma p-tau217 differentiate preclinical and prodromal cases, and that increases over time are associated with clinical progression in predementia AD. Repeated blood-based measurements of this marker could provide an accessible way to distinguish individuals who remain cognitively stable from those who experience cognitive deterioration, which will be essential for prioritizing access to disease-modifying therapies. Moreover, longitudinal monitoring of plasma p-tau217 could provide valuable insights into disease progression and therapeutic efficacy. Finally, we strongly argue that plasma p-tau biomarkers should be interpreted within the appropriate clinical context, rather than used for purely biological diagnosis.

Amyloid PET in Clinical Practice

Tomaž RUS, MD, PhD

Introduction

In recent years, the diagnosis of Alzheimer's disease (AD) has undergone a major paradigm shift from a purely clinical, syndrome-based approach to a biological diagnosis grounded in biomarkers, as articulated in the NIA–AA framework and its subsequent updates[1–4]. This transformation has fundamentally reshaped cognitive neurology and enabled the development and clinical implementation of disease-modifying therapies targeting core AD pathology.

Cerebrospinal fluid (CSF) biomarkers of AD were first investigated in the 1990s and entered widespread clinical use during the 2010s [5]. Imaging biomarkers capable of detecting brain amyloid pathology emerged approximately two decades later, beginning with the first successful in vivo studies using Pittsburgh Compound-B (PiB) in the early 2000s and progressing to routine clinical use in the late 2010s and early 2020s [6]. Today, both CSF biomarkers and amyloid PET represent key tools for the in vivo detection of amyloid-β pathology and allow the selection of appropriate patients for anti-amyloid therapies.

Radiopharmaceuticals and Detection of Amyloid In Vivo

Amyloid-β is characterized by a high β-pleated sheet secondary structure stabilized by hydrogen bonds and hydrophobic interactions. This structure confers high affinity for lipophilic, planar aromatic molecules. Based on histological dyes such as thioflavin T, 11C-PiB was the first compound shown to bind amyloid plaques in vivo and enable their visualization by PET imaging [6].
However, owing to the short half-life of 11C (≈20 minutes), clinical implementation of PiB was limited to centers with an on-site cyclotron. This limitation led to the development of three 18F-labeled tracers with longer half-lives, suitable for routine clinical distribution and use: 18F-flutemetamol, 18F-florbetaben, and 18F-florbetapir . 18F emits positrons that are detected by PET systems, allowing imaging with high spatial resolution and reliable assessment of cerebral amyloid burden.

Indications for Amyloid PET

According to the revised diagnostic criteria of the Alzheimer's Association, both CSF amyloid biomarkers and amyloid PET are valid and sufficient for the biological diagnosis of Alzheimer's disease. Importantly, however, amyloid PET is significantly less accessible worldwide, including in high-income countries, and is substantially more expensive than CSF testing without providing superior diagnostic accuracy. Consequently, clinicians and patients must carefully weigh the advantages and limitations of each modality [3].

The 2025 Updated Appropriate Use Criteria issued by the Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging define amyloid PET as a clinically mature but strictly indication-driven tool that should be used selectively rather than routinely [7]. Amyloid PET is recommended in patients with objective cognitive impairment (mild cognitive impairment or mild dementia) when AD is suspected but remains diagnostically uncertain after comprehensive specialist evaluation, or when confirmation of amyloid pathology is required to determine eligibility for disease-modifying anti-amyloid therapies. Conversely, amyloid PET is not recommended as a screening test in asymptomatic individuals, for routine confirmation of an already clear clinical diagnosis, or in situations where results would not influence clinical management [7].

With regard to CSF biomarkers, the recommendations acknowledge that CSF amyloid markers assess the same amyloid-β pathophysiological process and are often more accessible and cost-effective; therefore, CSF testing is considered an appropriate alternative in many clinical contexts.

Amyloid PET retains a complementary role when topographic information is required or when CSF biomarkers are contraindicated, unavailable, or inconclusive. In everyday clinical practice, amyloid PET is therefore frequently used when lumbar puncture is contraindicated (e.g., due to anticoagulant therapy) or technically not feasible.

Reading and Interpretation of Amyloid PET Scans

Amyloid PET radiopharmaceuticals are lipophilic, planar aromatic molecules that bind to β-sheet-rich amyloid plaques but also exhibit non-specific binding to other lipophilic structures, particularly myelin, which is abundant in white matter. Consequently, all amyloid PET scans show high physiological white-matter uptake, and accurate interpretation requires experience and focused assessment of the cortical grey matter, which may be challenging in the presence of cerebral atrophy.
A negative amyloid PET scan is often described metaphorically as a tree in winter, where only the white-matter "branches" are visible, whereas a positive scan resembles a tree in summer, with dense cortical "foliage" obscuring the underlying white-matter pattern. Each tracer manufacturer provides tracer-specific recommendations and reader training; for 18F-flutemetamol, currently used at UKC Ljubljana, standardized visual interpretation guidelines are followed [8].

Regions Assessed and Visual Classification (Standardized Interpretation)

A negative amyloid PET scan indicates none or only sparse cortical β -amyloid neuritic plaques, whereas a positive scan indicates a moderate to frequent plaque density. Images are reviewed visually using standardized color scales (Sokoloff, Rainbow, or Spectrum) by comparing cortical grey-matter uptake with adjacent white-matter uptake. Systematic assessment proceeds from the level of the pons upward and includes the frontal lobes and anterior cingulate, posterior cingulate and precuneus, temporoparietal cortex and insula, lateral temporal lobes, and the striatum. A region is considered negative if cortical uptake is clearly lower than white matter and similar to cerebellar cortex; it is considered positive if cortical uptake approaches or exceeds white-matter intensity. If any predefined cortical region is clearly positive, the scan is classified as positive overall. Cerebral atrophy may complicate interpretation because of partial-volume effects, and correlation with MRI or CT is therefore strongly recommended to improve diagnostic accuracy [8].

Diagnostic Accuracy of Amyloid PET versus CSF Amyloid Biomarkers

Meta-analytical evidence indicates that amyloid PET and cerebrospinal fluid (CSF) amyloid biomarkers provide comparable diagnostic accuracy for Alzheimer's disease. In a large meta-analysis by Olsson et al., amyloid PET demonstrated high sensitivity and specificity for detecting cerebral amyloid pathology, while CSF Aβ42 showed similar sensitivity but somewhat lower specificity when used alone; however, the use of CSF biomarker ratios (such as Aβ42/40 or Aβ42/tau) markedly improved specificity to levels comparable with amyloid PET. Importantly, no meaningful advantage of combining CSF and PET biomarkers was observed, supporting the conclusion that either modality can be used for biological diagnosis of Alzheimer's disease, with the choice guided primarily by availability, cost, invasiveness, and patient-specific considerations rather than differences in diagnostic performance [9].

Conclusion

Amyloid PET has become an established and biologically meaningful imaging biomarker in Alzheimer's disease, reflecting the broader shift toward biomarker-based diagnosis and treatment selection. Current evidence and guidelines support its use as a targeted, indication-driven tool, offering diagnostic value comparable to CSF amyloid biomarkers but at higher cost and lower accessibility. Accordingly, amyloid PET is best applied selectively—when diagnostic uncertainty persists, when spatial information is clinically relevant, or when CSF testing is contraindicated or inconclusive—while CSF biomarkers remain a widely accessible and cost-effective alternative. Optimal clinical practice therefore relies not on prioritizing one modality universally, but on thoughtful integration of amyloid PET and CSF biomarkers according to the specific clinical question, patient characteristics, and resource availability.

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Implementation of Amyloid-Targeting Therapies in Cognitive Clinics: Lessons Learned After 2 Years of Real-World Experience

Noa BREGMAN, MD

Abstract

The introduction of amyloid-targeting therapies (ATTs) has marked a major shift in the care of patients with early Alzheimer's disease (AD). These treatments offer, for the first time, disease-modifying potential in routine clinical practice, but they also require a level of diagnostic precision, logistical coordination, and safety monitoring that most cognitive clinics were not originally designed to provide. Over the past two years, our center has developed a structured multidisciplinary pathway for identifying eligible patients, confirming diagnosis, organizing treatment, and monitoring safety in real-world practice. This experience has shown that successful implementation depends not only on drug availability, but also on triage systems, biomarker access, MRI capacity, infusion infrastructure, and dedicated coordination staff. Early real-world data from our center suggest that ATTs can be delivered safely and effectively in practice, with ARIA rates broadly consistent with trial data, while also highlighting the importance of patient selection and baseline imaging characteristics. The lessons learned may help other cognitive clinics preparing to integrate these therapies into routine care.

Introduction

ATTs are changing the landscape of AD care. For many years, treatment in AD was largely symptomatic, with relatively limited monitoring requirements and often slow, non-urgent clinical pathways. In contrast, the use of monoclonal antibodies directed against amyloid requires a fundamentally different model: early identification of suitable patients, biomarker confirmation of AD pathology, structured safety assessment, repeated MRI surveillance, close post-infusion follow-up, and ongoing communication with patients and families.

This is therefore not simply the addition of a new medication to an existing clinic. It is a reorganization of the entire care pathway. The implementation of ATTs demands that cognitive neurology services function more like coordinated treatment programs than traditional diagnostic clinics. In our experience at Tel Aviv Sourasky Medical Center (TLVMC), the central challenges can be grouped into four domains: finding the right patients, completing the work-up efficiently, organizing administration, and ensuring safe longitudinal monitoring.

Finding the right patients

The first challenge is identifying patients who are both clinically appropriate and likely to benefit. Cognitive complaints in older adults are extremely common, but their causes are heterogeneous. Real-world implementation therefore begins with triage. In our center, referrals are received from community neurologists, family physicians, psychiatrists, and geriatricians. These referrals are reviewed by a clinical nurse coordinator, who prioritizes patients with a high suspicion of early-stage AD and verifies that the referral includes a basic neurological and cognitive evaluation, brain imaging, and reasonable exclusion of alternative causes.

This step is crucial. Even before treatment decisions are discussed, cognitive clinics face limited capacity, and prioritization becomes essential. Patients who are most likely to meet clinical and biomarker criteria for treatment are scheduled earlier, while clinic capacity is adjusted to improve access for potentially eligible cases. In practice, one of the most important lessons we learned is that implementation starts well before the infusion unit: it starts with referral quality, triage discipline, and the ability to recognize the right stage of disease.

Streamlining the diagnostic work-up

Once patients reach the cognitive neurology unit, the next goal is to complete diagnostic confirmation as efficiently as possible. In our current model, the first visit focuses on completing missing history, neurological examination, and cognitive assessment as needed, defining the clinical syndrome, and initiating etiological work-up for suspected early AD. This includes brain MRI, AD biomarker testing by lumbar puncture or amyloid PET, and APOE-related counseling with referral for genotyping. In selected cases, blood biomarkers are also incorporated into the diagnostic pathway.

One of the major operational lessons from our early experience was that sequential diagnostic steps create unacceptable delays. We therefore shifted from an initial three-visit structure to a more efficient two-visit model. In this updated workflow, biomarker testing and APOE evaluation are initiated in parallel at the first visit, and complex cases are discussed in a multidisciplinary team meeting before the second visit, where diagnosis and treatment planning are reviewed with the patient and family. This parallelization significantly reduces time to decision-making and is especially important in a setting where patients may otherwise wait months for each individual component of the work-up.

Building the infrastructure

A major lesson from real-world implementation is that ATT programs require dedicated infrastructure. At our center, treatment delivery depends on close collaboration between cognitive neurologists, a unit nurse, a clinical coordinator, neuroradiologists, neuropsychologists, research coordinators, a social worker, the day-admission infusion unit, the genetic laboratory, and the neuroimmunology laboratory. The service currently includes approximately 4.5 neurologist full-time equivalents involved in patient management, alongside a dedicated clinical coordinator and neuroradiology support for ARIA surveillance.

The importance of coordination cannot be overstated. The clinical coordinator plays a pivotal role in maintaining direct contact with patients, scheduling treatments and follow-up visits, organizing MRI studies, tracking side effects, and communicating with nursing staff, pharmacy, neuroradiology, and the infusion unit. In parallel, administrative support is needed for insurance approvals, clinical documentation, and research data entry. In many ways, this role is the operational backbone of the program. Without such coordination, even strong clinical decision-making becomes difficult to translate into safe and scalable treatment delivery.

Solving real-world bottlenecks

Implementation in practice quickly reveals bottlenecks. In our experience, the biomarker stage was often the rate-limiting step. Lumbar puncture capacity was initially limited, so additional afternoon sessions were opened in the neurology day-admission unit. Amyloid PET was also constrained, particularly before in-house availability improved through collaboration with nuclear medicine. For this reason, PET has generally been reserved for selected cases, such as contraindication to lumbar puncture, inconclusive results, or patient preference.

APOE genotyping created a different challenge: the limited availability of formal genetic counseling. Our solution was to train treating neurologists to provide focused counseling and communicate APOE results directly, while fast-tracking testing through the genetic laboratory. Baseline MRI interpretation posed another practical problem, since many scans were performed externally. To address this, imaging is uploaded by the clinical coordinator into the hospital system and reviewed by trained neuroradiologists, who issue focused reports addressing treatment contraindications and later ARIA surveillance. These workflow adaptations illustrate a broader point: ATT implementation is less about a single innovation and more about many small operational improvements across the pathway.

Administration and monitoring

Treatment administration itself requires preparation. Capacity in the day-admission unit was addressed before ATT delivery began, and with growing patient numbers, afternoon infusion sessions were added to allow further expansion. Monitoring begins immediately after infusion, with a nurse phone call within 24 hours to assess adverse symptoms. MRI surveillance is then performed according to protocol, and wherever possible scans are obtained in-house on the same scanner to improve consistency in ARIA detection. External scans are performed on consistent machines and reviewed centrally by the neuroradiology team, with results typically available within 48 hours and then reviewed by the treating neurologist before treatment continuation is approved.

This structured follow-up is one of the defining differences between ATT programs and earlier dementia care models. It requires not only imaging access but also rapid reporting, clinician availability, and clear communication channels. In our experience, safe monitoring depends on system design rather than on individual effort alone.

Early real-world outcomes

Between November 2023 and April 2026, 146 patients with biomarker-confirmed early Alzheimer's disease initiated treatment with lecanemab at our center. The cohort had a mean age of 72.9 ± 7.3 years, 51.0% were women, and 57.0% were APOE ε4 carriers, consistent with a typical real-world early ADpopulation.

We collaborated with icometrix to find AI-derived MRI predictors of benefit and ARIA in real-world lecanemab treatment. Our cohort included 82 biomarker-confirmed patients with early AD treated between November 2023 and June 2025; most had MCI, a smaller proportion had mild dementia, the mean baseline MMSE was 24.1, and 58.5% were APOE ε4 carriers. Forty-four patients completed 12 months of follow-up, with a mean MMSE decline of 2.5 points and marked inter-individual variability. This heterogeneity is clinically important, because it suggests that the same treatment may have different effects depending on baseline disease burden and brain reserve.

One of the more informative observations from our cohort was that greater baseline grey matter volume was associated with less MMSE decline over 12 months, independent of age, sex, and baseline MMSE. This supports the concept that structural brain integrity may influence treatment response and reinforces the importance of not waiting too long before initiating disease-modifying therapy in appropriate patients. At the same time, baseline imaging in many patients already showed substantial neurodegeneration despite an early clinical stage, highlighting the mismatch that often exists between symptoms and biological severity in routine practice.

ARIA occurred in approximately 20.7% of patients in the lecanemab cohort, with the majority of events asymptomatic and predominantly ARIA-H, broadly consistent with clinical trial experience. Baseline microhemorrhage burden emerged as the strongest predictor of ARIA, with each additional microhemorrhage increasing risk substantially, whereas APOE ε4 showed only a directional trend in this cohort. Importantly, AI-supported microhemorrhage quantification showed excellent agreement with expert human ratings, supporting the feasibility of scalable quantitative MRI support in clinical care.

Our early donanemab experience, beginning in 2025, shows similar operational themes. In the first 46 treated patients, the cohort was again predominantly early-stage and amnestic, with biomarker confirmation mainly based on CSF and a smaller contribution from amyloid PET and blood biomarkers. ARIA occurred in roughly one fifth of patients and was mostly mild, again emphasizing that structured monitoring programs are essential from the outset. These data remain early, and follow-up duration is not yet uniform across patients, but they reinforce the overall feasibility of implementation in a real-world cognitive clinic.

Conclusions

After two years of real-world experience, our main conclusion is clear: amyloid-targeting therapies can be implemented successfully in routine cognitive neurology practice, but only when supported by a structured multidisciplinary system. The key ingredients are careful patient selection, rapid access to biomarker confirmation, standardized MRI review, infusion capacity, and strong coordination throughout the pathway.

ATTs represent a new chapter in Alzheimer's care, but also a new obligation for healthcare systems. Clinics that wish to offer these therapies must move from an episodic diagnostic model to an integrated treatment model. In that transition, the most valuable lessons may be surprisingly practical: triage early, run work-up steps in parallel, centralize coordination, standardize imaging, and build safety monitoring into the system from day one. If these foundations are in place, real-world implementation is not only possible, but sustainable and clinically meaningful.

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Estimates of current capacity for diagnosing and implementation of new treatment of Alzheimer's disease in Slovenia

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Alzheimer's disease (AD) represents a growing public health challenge, particularly in aging societies. In Slovenia, it is estimated that more than 40 000 individuals were living with dementia, reflecting a steady increase compared to earlier estimates of 34 000 cases in 2018.[1,2] Projections suggest that this number will continue to rise and may double by 2050.[2] The associated societal and economic burden is substantial. Dementia is one of the leading causes of disability and dependency among older adults, requiring increasing levels of healthcare, social support, and informal care.[3] The annual economic burden of dementia in Slovenia is estimated at approximately staggering €370 million, with the majority of costs attributable to formal and informal long-term care.[4]

Until recently, treatment options for AD were limited to symptomatic therapies, contributing to underdiagnosis and reduced engagement with healthcare services. However, the emergence of disease-modifying therapies (DMTs), such as lecanemab and donanemab, marks a major shift in the field. These therapies target amyloid pathology and have demonstrated a modest but clinically meaningful slowing of cognitive decline in early stages of the disease.[5,6] Lecanemab received a marketing authorization by the European Commission in April 2025 and donanemab in September 2025.[7,8]

While these developments offer new hope, they also introduce significant challenges. DMTs require early diagnosis, confirmation of Alzheimer's pathology, and complex monitoring, placing substantial demands on healthcare systems. Slovenia, with a population of approximately 2.1 million, has a highly centralized healthcare system with limited specialized capacity for cognitive disorders. This raises important questions regarding system readiness for the implementation of DMTs.

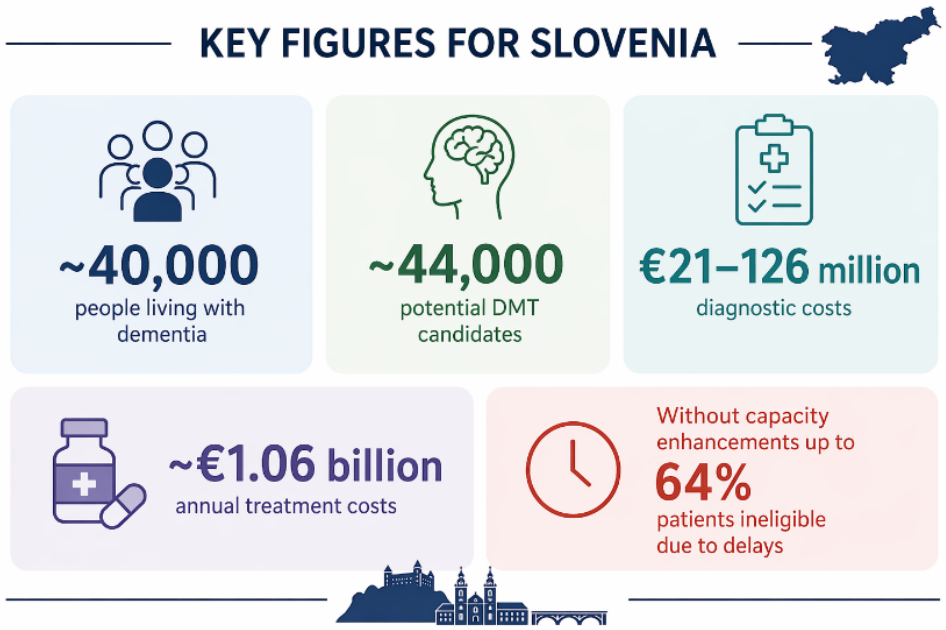

Figure 1: *Dementia in Slovenia: key metrics*

Real-world diagnostic capacity

In a previous study, we analyzed real-world data from the Centre for Cognitive Impairments at the University Medical Centre Ljubljana between 2021 and 2022. Over a two-year period, 1,461 initial visits and 657 lumbar punctures were performed in patients with cognitive complaints. Among these, 246 individuals had a cerebrospinal fluid (CSF) biomarker profile consistent with AD. However, only 114 patients were identified at the stage of mild cognitive impairment (MCI) or mild dementia, making them potential candidates for disease-modifying therapy.[9] In 2024, there were 279 lumbar punctures out of which 132 were consistent with AD.

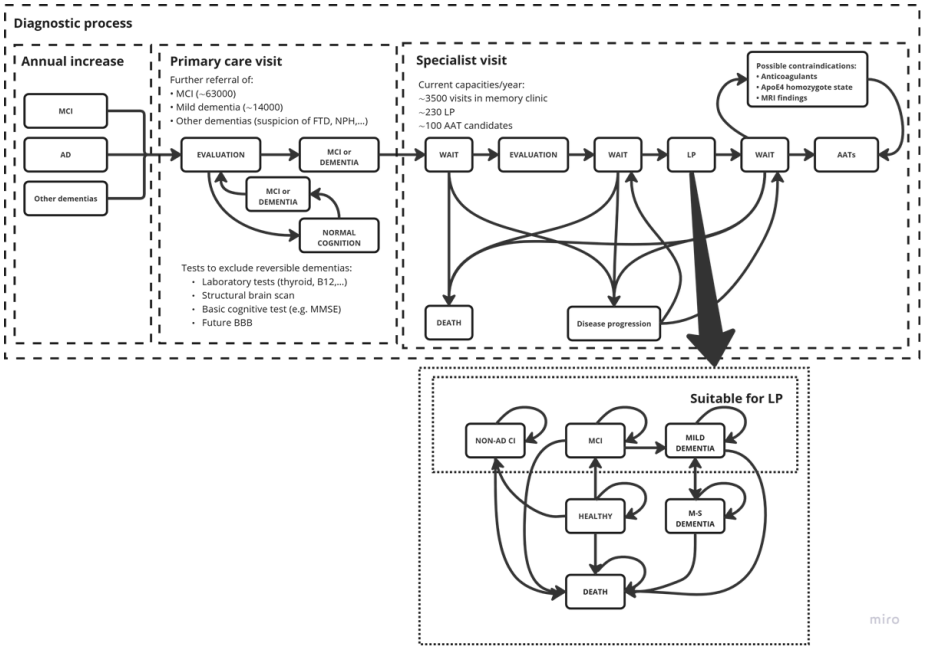

Figure 2: Diagram of patient flow through the medical system and current capacities.
Adapted from Zupanic et al. Estimates of current capacity for diagnosing and implementation of new treatment Alzheimer's disease in Slovenia. 2026. License: Creative Commons CC BY-NC 4.0.

National estimates

Based on epidemiological data, we estimated that approximately 44,000 individuals in Slovenia could be eligible for DMTs, including patients with MCI due to AD and those in the mild AD stage.[10, 11]

To further explore healthcare system readiness, we developed a model simulating patient flow under different scenarios. The results demonstrate significant bottlenecks, particularly in access to specialist evaluation and CSF diagnostics. Under current real-life conditions, waiting times for specialist visits could extend to approximately 1.8 years, while waiting times for lumbar puncture and CSF analysis could reach up to 18 years.[11]

These delays have major clinical consequences. During the waiting period, a substantial proportion of patients progress to more advanced stages of disease or die, becoming ineligible for treatment.

In our model, up to 64% of patients would no longer meet eligibility criteria by the time diagnostic confirmation is completed. Even with moderate increases in capacity, delays remain considerable, indicating that incremental improvements alone are insufficient.

The role of blood-based biomarkers

One of the most promising strategies to address diagnostic bottlenecks is the introduction of blood-based biomarkers. These tests have the potential to serve as a triage tool, allowing only selected patients to proceed to confirmatory CSF analysis.[12]

Our modelling suggests that integrating blood-based biomarkers could significantly reduce the burden on specialized services. When combined with increased system capacity, this approach represents the most feasible pathway for implementing DMTs in Slovenia. Waiting times for invasive diagnostics could be reduced to approximately 4 years, and the proportion of patients becoming ineligible for treatment could decrease to around 6%.[11]

Moreover, recent evidence suggests that only 8–15% of individuals with MCI or mild AD will ultimately meet eligibility criteria for new DMTs, underscoring the need for efficient pre-selection and triage.[13]

Conclusions

The introduction of DMTs for AD represents a major turning point in neurology. The main limiting factor is the ability to identify eligible patients in a timely manner. Diagnostic infrastructure—particularly for biomarker confirmation—represents the critical bottleneck.

Addressing these challenges will require substantial investment in healthcare infrastructure, workforce expansion, and reorganization of diagnostic pathways. At the same time, the introduction of DMTs provides an opportunity to improve overall dementia care, including earlier diagnosis, better disease characterization, and more structured patient management.

Ethical considerations are also important, as limited resources may restrict access to treatment. Furthermore, the burden on patients and caregivers—particularly given the need for repeated infusions and monitoring—should not be underestimated.

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From Science to Clinical Practice: Preparing Memory Clinics for the Era of Disease-Modifying Alzheimer's Therapies

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Abstract

Alzheimer's disease (AD) is entering a new therapeutic era in which disease-modifying therapies (DMTs), particularly anti-amyloid monoclonal antibodies for early symptomatic disease, are reshaping the role of memory clinics. These clinics are no longer solely diagnostic services but increasingly function as treatment gateways that must integrate early biomarker-based diagnosis, eligibility assessment, safety monitoring, and longitudinal follow-up. Biomarkers are now essential, but they must remain embedded in clinical judgement. Diagnostic evaluation should therefore stay stepwise, beginning with history taking from the patient and an informant, cognitive screening, assessment of daily functioning, exclusion of reversible causes, and a full neuropsychological examination. In many European settings, cerebrospinal fluid biomarkers remain central to confirming AD pathology. Among blood-based biomarkers, plasma P-tau217 appears most promising as a triage tool in specialist memory clinics. A two-cut-off strategy may improve efficiency by identifying likely amyloid-positive and amyloid-negative individuals while reserving cerebrospinal fluid or amyloid-PET testing for intermediate cases. Successful implementation of DMTs will depend not only on biomarkers, but also on well-organised, multidisciplinary memory clinics capable of delivering safe, equitable, and integrated care.

Introduction

The field of Alzheimer's disease (AD) is undergoing a profound transition. For decades, memory clinics mainly offered clinical assessment, biomarker-based diagnosis, counselling, and symptomatic treatment. The emergence of disease-modifying therapies (DMTs), particularly anti-amyloid monoclonal antibodies for early symptomatic AD, changes that paradigm. In this new landscape, memory clinics are no longer only diagnostic services; they are becoming treatment-gateways that must combine early biomarker-based diagnosis, safety monitoring, and longitudinal follow-up [1–4].

This shift is important not only because new therapies have become available, but because they require a different standard of diagnostic precision. In routine practice, eligibility for anti-amyloid treatment depends on more than a compatible clinical syndrome. It also requires biomarker confirmation of amyloid pathology, structured exclusion of competing diagnoses, assessment of comorbidity and frailty, MRI-based safety screening, and careful counselling about expected benefit and risk [1,3,5,6].

At the same time, the biological understanding of AD has advanced. Rather than viewing AD as a late-stage dementia syndrome, it is now understood as a long pathobiological continuum in which amyloid deposition, tau aggregation, synaptic dysfunction, and neurodegeneration evolve over years before dementia becomes clinically overt [1,7,8]. That conceptual shift matters clinically: therapies aimed at slowing disease progression are most relevant in early symptomatic phases, where the balance between potential benefit, treatment burden, and safety can still be favourable [2,5,6].

The central challenge for contemporary dementia care is therefore translational: how do we move from scientific progress to safe and equitable clinical implementation? The answer lies in biomarker-based diagnosis embedded within well-organised memory clinics. The aim of this brief overview is to summarise the main principles that should guide this transition, with particular attention to blood-based biomarkers and the practical adaptations memory clinics must make in the era of DMTs.

Clinical context comes first

Although biomarkers have become essential, they must not replace clinical judgement. A central message of recent European and Belgian consensus work is that biomarker testing should be performed only in individuals with objective cognitive decline and a reasonable clinical

suspicion of AD [3,4]. Amyloid positivity alone does not establish a clinical diagnosis of AD, particularly in older adults and in patients with non-amnestic syndromes, because amyloid positivity becomes more common with age and may coexist with other neurodegenerative or vascular pathologies [3,7,9].

In practice, the diagnostic work-up should remain stepwise. It begins with history taking from patient and an informant, cognitive screening, assessment of daily functioning, and the exclusion of reversible or contributing causes. A full neuropsychological examination is especially valuable in early symptomatic disease because it helps distinguish normal ageing from mild cognitive impairment (MCI), clarifies the cognitive profile, and supports syndromic diagnosis [3,10,11]. Structural brain imaging—preferably MRI—remains indispensable. It helps excluding structural lesions, evaluates vascular co-pathology, and, crucially in the DMT era, identifies markers relevant for treatment safety such as microbleeds and superficial siderosis [3,5,6].

This “clinical context first” principle protects against mis- and overdiagnosis. Biological frameworks have great value for research, prevention trials, and disease staging, but for routine practice the most clinically meaningful approach remains a clinical-biological construct: a compatible syndrome supported by biomarkers, rather than biomarkers interpreted in isolation [3,7].

Biomarker-based diagnosis in the DMT era

Biomarkers now play a central role because they allow in vivo confirmation of the biological process underlying symptoms. The current diagnostic armamentarium includes cerebrospinal fluid (CSF) biomarkers, amyloid-PET, tau-PET, and blood-based biomarkers [3,4].

CSF biomarkers remain a cornerstone of biomarker-based diagnosis in many European settings. Reduced CSF Aβ1-42, particularly when interpreted as the Aβ1-42/Aβ1-40 ratio, reflects cerebral amyloid deposition; increased P-tau181 reflects downstream tau phosphorylation; and total tau (T-tau) reflects neuronal degeneration [3,12,13]. When amyloid and tau markers are both abnormal in a patient with early cognitive symptoms, the specificity for AD is high. CSF is often the most practical first-line confirmatory test in specialist clinics, provided that local pre-analytical and analytical quality standards are robust [3].

Amyloid-PET offers a non-invasive alternative for confirming amyloid status. It is especially useful when lumbar puncture is not feasible, is contraindicated, or has yielded inconclusive results [3]. Tau-PET is more recent and may prove particularly helpful in atypical phenotypes, discrepant cases, and disease staging, but at this moment, it still is a research instrument [3,4]. FDG-PET also retains diagnostic value in differential diagnosis, especially when clinical findings and amyloid biomarkers are not fully aligned [3].

The key clinical point is not simply to accumulate tests, but to place them in an ordered pathway. Biomarkers should be used to resolve uncertainty, confirm the likely pathology in symptomatic patients, and support treatment decisions. In that sense, DMTs have made clinical reasoning more important than ever, because the consequences of diagnostic error are greater.

Blood-based biomarkers: promise, pragmatism, and limits

Blood-based biomarkers offer a less invasive, more scalable, and potentially more cost-effective alternative to CSF testing and PET imaging [3,14]. Of the currently available plasma markers, P-tau217 has the strongest evidence base. Across well-characterised cohorts, it shows high concordance with CSF and amyloid-PET and achieves strong diagnostic performance for detecting AD pathology [3,15,16].

The most plausible near-term role for plasma P-tau217 is as a triage tool in specialist memory clinics, not as a stand-alone population screening test [3,17]. Recent recommendations support a two-cut-off strategy: values above a higher cut-off suggest amyloid positivity, values below a lower cut-off suggest amyloid negativity, and intermediate results trigger confirmatory CSF or amyloid-PET testing [3,14,17,18]. This approach is attractive because it can reduce the need for invasive or expensive second-line testing while preserving diagnostic safety.

Plasma biomarkers are highly dependent on pre-test probability. Their performance is best when applied in symptomatic patients evaluated in memory clinics [3,14,19]. Assay standardisation, platform comparability, and inter-laboratory reproducibility remain important barriers to fully harmonised implementation. In addition, kidney function may influence test interpretation [3,19]. For these reasons, blood-based biomarkers should currently be integrated into multidisciplinary pathways rather than used in isolation. At this stage, its use should be confined to memory clinics in order to avoid mis- and overdiagnosis.

The practical conclusion is straightforward: blood-based biomarkers are likely to expand access and shorten diagnostic pathways, but their safest current role is in specialist memory clinics with access to confirmatory CSF or PET, structured interpretation, and multidisciplinary decision-making [3,14].

How memory clinics must adapt

If biomarkers provide the diagnostic backbone of the DMT era, memory clinics provide the organisational backbone. Implementing DMTs requires more than identifying amyloid positivity. It requires clinics that can deliver an integrated pathway from referral to eligibility assessment, treatment initiation, monitoring, and long-term follow-up [3].

First, memory clinics need explicit diagnostic algorithms. These should define which patients are suitable for blood-based triage, when to proceed to CSF or amyloid-PET, how to handle discordant results, and how to integrate neuropsychology, MRI, and differential diagnosis into treatment selection. Such algorithms must also incorporate "stopping points," because many patients seen in clinical practice will not be appropriate candidates for anti-amyloid therapy due to advanced disease stage, absence of amyloid pathology, frailty, contraindications, or safety concerns [3,5,6].

Second, MRI capacity becomes strategically important. In the DMT era, MRI is not only part of dementia work-up; it is also mandatory for ARIA risk stratification and follow-up. Clinics therefore require standardised MRI protocols, reliable access to scanners, and radiological expertise in detecting microbleeds, siderosis, and other relevant markers [3,5,6]. Likewise, APOE genotyping and pre- and post-test counselling become clinically relevant in treatment candidates because APOE ε4 status influences ARIA risk and, in Europe, may affect treatment eligibility [3,5,6].

Third, multidisciplinary collaboration must intensify. Dementia care can no longer be organised as a series of isolated assessments. Neurologists, geriatricians, psychiatrists, neuropsychologists, specialist nurses, radiologists, nuclear medicine physicians, laboratory specialists, and where appropriate genetics professionals need shared workflows and clear responsibilities [3]. In older adults, comprehensive geriatric assessment may be particularly helpful in weighing expected benefit against frailty, comorbidity, treatment burden, and the feasibility of repeated imaging and infusions [3].

Fourth, patient counselling requires more time and greater nuance. The currently available DMTs are not curative. They offer modest slowing of progression in selected patients, at the cost of treatment burden and the possibility of adverse events, particularly ARIA [2,5,6]. Memory clinics therefore need processes for shared decision-making that address realistic expectations, uncertainty, treatment logistics, safety monitoring, and the emotional implications of biomarker and genetic testing [3,10].

Finally, memory clinics should function as learning systems. Real-world data on eligibility, safety, treatment discontinuation, outcomes, and patient-reported experience will be essential for refining pathways over time. This is especially important because trial populations do not fully capture the heterogeneity of routine care [3,4].

Equity, capacity, and the future of dementia care

The arrival of DMTs also exposes longstanding weaknesses in dementia care systems. Even well-developed healthcare systems often lack sufficient diagnostic capacity, equitable access to memory clinics, reimbursement for biomarker testing, and workforce capacity, especially in neuropsychology [3]. Blood-based biomarkers may help address part of this bottleneck by improving triage efficiency, but they cannot substitute for broader system preparedness.

A further point is that most people with AD may still not receive anti-amyloid treatment, whether because they present too late, have contraindications, are APOE ε4 homozygotes under European restrictions, or have substantial mixed pathology or frailty [3]. For these individuals, high-quality dementia care remains just as important. The DMT era should therefore not narrow the mission of memory clinics, but it should broaden their role as centres for diagnosis, counselling, risk communication, supportive care, and coordinated long-term management.

Conclusions

The era of disease-modifying therapy has transformed AD from late clinical diagnosis and symptomatic management into one that requires early, biomarker-based, personalised and precision care. Biomarker-based diagnosis is central to that transformation, but it must remain rooted in clinical context. CSF and PET continue to provide robust confirmatory information, while blood-based biomarkers—especially plasma P-tau217—make diagnostic pathways more scalable when used in specialist settings [3,14,15].

Ultimately, the success of DMT implementation will depend on structured pathways, MRI and laboratory capacity, multidisciplinary governance, careful counselling, and a sustained commitment to equitable access. The translation from science to clinical practice is no longer a future aspiration; it is a present organisational challenge. Meeting that challenge well may be one of the most important advances in dementia care of the coming decade.

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AD - Alzheimerjeva bolezen; **APOE ε4 -** apolipoprotein E ε4
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Skrajšan povzetek glavnih značilnosti zdravila LEQEMBI: Ime zdravila in sestava: LEQEMBI 100 mg/ml koncentrat za raztopino za infundiranje. En mililiter koncentrata vsebuje 100 mg lekanemaba. **Indikacije:** Za zdravljenje odraslih bolnikov s klinično diagnozo blage kognitivne motnje in blage demence zaradi Alzheimerjeve bolezni (zgodnja Alzheimerjeva bolezen), ki niso nosilci ali so heterozigotni nosilci apolipoproteina E ε4 (ApoE ε4), s potrjenim patološkim amiloidom. **Odmerjanje in način uporabe:** Zdravljenje morajo uvesti in nadzorovati zdravniki, ki imajo izkušnje z diagnosticiranjem in zdravljenjem Alzheimerjeve bolezni ter lahko zagotovijo pravočasen dostop do magnetnoresonančnega (MR) slikanja. Lekanemab morajo infundirati kvalificirani zdravstveni delavci, ki so usposobljeni za spremljanje, prepoznavanje in obvladovanje z infuzijo povezanih reakcij. • Priporočeni odmerek lekanemaba je 10 mg/kg telesne mase v obliki intravenske (i.v.) infuzije vsaka 2 tedna. Zdravljenje z lekanemabom je treba prekiniti, ko Alzheimerjeva bolezen pri bolniku napreduje v zmerno hudo obliko. Med zdravljenjem z lekanemabom je treba približno vsakih 6 mesecev opraviti testiranje kognitivnih funkcij in oceniti klinične simptome. Na podlagi testiranja kognitivnih funkcij in napredovanja simptomov je treba oceniti, ali je Alzheimerjeva demenca pri bolniku napredovala v zmerno hudo obliko oziroma ali siceršnji klinični potek kaže na to, da lekanemab pri bolniku ni učinkovit. • Lekanemab je samo za intravensko uporabo. Lekanemab se daje v obliki približno 1-urne intravenske infuzije vsaka 2 tedna. Pri prvem infundiranju je treba bolnika še približno 2,5 ure po končanem infundiranju opazovati glede znakov in simptomov z infuzijo povezanih reakcij. Lekanemab je pred intravenskim infundiranjem treba razredčiti. **Posebne populacije:** Prilagajanje odmerka pri bolnikih, starih ≥ 65 let, ni potrebno. Posebno prilagajanje odmerka pri bolnikih z blago do zmerno okvaro ledvic ni potrebno. Posebno prilagajanje odmerka pri bolnikih z blago do zmerno okvaro jeter ni potrebno. Lekanemab ni namenjen za uporabo pri pediatrični populaciji. **Kontraindikacije:** Preobčutljivost na učinkovino ali katero koli pomožno snov. Bolniki z motnjami strjevanja krvi, ki niso ustrezno urejene. Predhodna znotrajmožganska krvavitev, več kot 4 mikrokrvavitve, površinska sideroza ali vazogeni edem ali druge spremembe, ki kažejo na cerebralno amiloidno angiopatijo (CAA), odkrite pri MR slikanju pred zdravljenjem. Zdravljenje z lekanemabom se ne sme uvesti pri bolnikih, ki že prejemajo antikoagulacijsko zdravljenje. **Opozorila/previdnostni ukrepi:** Za zagotovitev varne in učinkovite uporabe je treba zdravljenje pri vseh bolnikih uvesti preko sistema centralnega registra, vzpostavljenega v okviru programa nadzorovanega dostopa. Z namenom izboljšanja sledljivosti bioloških zdravil je treba jasno zabeležiti ime in številko serije uporabljenega zdravila. Pri bolnikih, ki so se zdravili z lekanemabom, so se pojavile preobčutljivostne reakcije, vključno z angioedemom, bronhospazmom in anafilaksijo, ki so lahko resne. Ob prvem pojavu katerih koli znakov ali simptomov, ki kažejo na preobčutljivostno reakcijo, takoj prekinite infundiranje in uvedite ustrezno zdravljenje. Pred začetkom zdravljenja je treba z ustreznim testom potrditi prisotnost patološkega amiloida beta. Pri bolnikih z Alzheimerjevo boleznijo se lahko spontano pojavijo z amiloidom povezane nepravilnosti pri slikovnih preiskavah (ARIA). ARIA se običajno pojavijo v zgodnji fazi zdravljenja in so največkrat asimptomatske, redko pa se lahko pojavijo tudi resni in življenjsko ogrožajoči dogodki, vključno z epileptičnim napadom in epileptičnim statusom. Kadar so prisotne ARIA, lahko bolniki poročajo o simptomih, ki vključujejo glavobol, zmedenost, spremembe vida, omotico, navzeo in težave pri hoji. Pojavijo se lahko tudi žariščni nevrološki izpadi. Tveganje za ARIA je večje pri homozigotnih nosilcih apolipoproteina E ε4 (ApoE ε4). Poleg ARIA so se pri bolnikih, ki so se zdravili z lekanemabom, pojavile tudi znotrajmožganske krvavitve premera več kot 1 cm. Priporočljivo je pridobiti MR slike možganov ob izhodišču in nato opravljati redna kontrolna slikanja. Posebej skrbno klinično spremljanje glede ARIA je priporočljivo v prvih 14 tednih zdravljenja. Če se pri bolniku pojavijo simptomi, ki kažejo na ARIA, je potrebna klinična ocena, vključno z dodatnimi MR preiskavami. Pri bolnikih z asimptomatskimi radiografskimi ARIA z edemom (ARIA-E) je priporočljivo posebej skrbno klinično spremljanje glede simptomov ARIA. Po 1 do 2 mesecih (ali prej, če so prisotni simptomi) je treba opraviti dodatna MR slikanja in oceniti, ali so spremembe izzvenele. Pri bolnikih, ki se zdravijo z lekanemabom in so homozigotni nosilci gena ApoE ε4, se pogosteje pojavljajo ARIA, vključno s simptomatskimi resnimi in ponavljajočimi se ARIA. Lekanemab ni indiciran za uporabo pri bolnikih, ki so homozigotni nosilci. Pri bolnikih, ki so jemali tako lekanemab kot antikoagulante, in pri bolnikih, ki so med zdravljenjem z lekanemabom prejemali trombolitična zdravila, so opazili znotrajmožganske krvavitve premera več kot 1 cm, vključno s smrtnimi primeri. V kliničnih preskušanjih je bila uporaba antitrombotičnih zdravil ob izhodišču dovoljena, če je bolnik prejemal stabilen odmerek. Pri uporabi antiagregacijskih zdravil niso opazili povečanega tveganja za ARIA ali znotrajmožganske krvavitve. Ker so pri bolnikih, ki so jemali tako lekanemab kot antikoagulante, in pri bolnikih, ki so med zdravljenjem z lekanemabom prejemali trombolitična zdravila, opazili znotraj možganske krvavitve, je pri odločanju glede uporabe antikoagulantov ali trombolitičnih zdravil pri bolnikih, ki se že zdravijo z lekanemabom, potrebna dodatna previdnost. Če je med zdravljenjem z lekanemabom treba uvesti antikoagulacijsko zdravljenje, je treba zdravljenje z lekanemabom začasno prekiniti. Zdravljenje z lekanemabom se lahko nadaljuje, ko za antikoagulacijsko zdravljenje ni več medicinskih indikacij. Sočasna uporaba acetilsalicilne kisline in drugih antiagregacijskih zdravil je dovoljena. Uporabi trombolitičnih zdravil se je treba izogibati, razen v primeru neposredno življenjsko ogrožajočih indikacij, ki jih ni mogoče zdraviti na drug način, če bi bile koristi lahko večje od tveganj. Ker lahko ARIA-E povzročijo žariščne nevrološke izpade, ki lahko posnemajo ishemično možgansko kap, morajo lečeči zdravniki presoditi, ali bi bili ti simptomi lahko posledica ARIA-E, preden bolniku, ki se zdravi z lekanemabom, predpišejo trombolitično zdravilo. Zdravljenje z lekanemabom se ne sme uvesti pri bolnikih, ki že prejemajo antikoagulacijsko zdravljenje. Prisotnost alela ApoE ε4 je povezana s CAA, pri kateri obstaja povečano tveganje za znotrajmožganske krvavitve. V kliničnih preskušanjih z lekanemabom so opazili z infuzijo povezane reakcije, ki so bile večinoma blage ali zmerne in so se pojavile pri prvem infundiranju. V primeru z infuzijo povezane reakcije je treba zmanjšati hitrost infundiranja ali prekiniti infundiranje in uvesti ustrezno zdravljenje v skladu s kliničnimi indikacijami. Pred naslednjimi infundiranji je lahko smiselno uvesti profilaktično zdravljenje z antihistaminiki, acetaminofenom, nesteroidnimi protivnetnimi zdravili ali kortikosteroidi. Iz kliničnih preskušanj z lekanemabom so izključili bolnike s prehodnimi možganskimi ishemijami, možgansko kapjo ali epileptičnimi napadi v zadnjih 12 mesecih pred presejanjem. Varnost in učinkovitost pri teh bolnikih nista znani. Iz kliničnih preskušanj z lekanemabom so izključili bolnike z boleznimi imunskega sistema, ki niso bile ustrezno urejene ali jih je bilo treba zdraviti z imunoglobulini, sistemskimi monoklonskimi protitelesi, sistemskimi imunosupresivi ali plazmaferezo, zato varnost in učinkovitost pri teh bolnikih nista znani. Iz kliničnih preskušanj z lekanemabom so izključili bolnike z avtosomsko dominantno Alzheimerjevo boleznijo ali Downovim sindromom, ki sta lahko povezana s pogostejšim pojavljanjem CAA in dogodkov ARIA. Varnost in učinkovitost lekanemaba pri teh bolnikih nista znani. Zdravnik, ki bo predpisal zdravilo, se mora z bolnikom pogovoriti o tveganjih zdravljenja z lekanemabom, MR slikanjih in znakih ali simptomih neželenih učinkov ter o tem, kdaj mora bolnik poiskati pomoč zdravstvenega delavca. Bolnik bo prejel kartico za bolnika in navodila, da jo mora imeti ves čas pri sebi. **Neželeni učinki:** Zelo pogosti (≥ 1/10): glavobol, ARIA, ARIA z depoziti hemosiderina (ARIA-H), ≤ 10 možganskih mikrokrvavitev, z infuzijo povezane reakcije. Pogosti (≥ 1/100 do < 1/10): preobčutljivostne reakcije, zapoznele preobčutljivostne reakcije, simptomatske ARIA-H, > 10 možganskih mikrokrvavitev, površinska sideroza, ARIA-E, simptomatske ARIA-E, atrijska fibrilacija, navzea. Občasni (≥ 1/1000 do < 1/100): znotrajmožganska krvavitev premera > 1 cm. Poročanje o domnevnih neželenih učinkih zdravila po izdaji dovoljenja za promet je pomembno. Omogoča namreč stalno spremljanje razmerja med koristmi in tveganji zdravila. Od zdravstvenih delavcev se zahteva, da poročajo o katerem koli domnevnem neželenem učinku zdravila na Nacionalni center za farmakovigilanco, Slovenčeva ulica 22, SI-1000 Ljubljana, Tel: +386 (0)8 2000 500, Faks: +386 (0)8 2000 510, e-pošta: h-farmakovigilanca@jazmp.si, spletna stran: www.jazmp.si. **Način izdajanja zdravila:** H **Imetnik dovoljenja za promet:** Eisai GmbH, Edmund-Rumpler-Straße 3, 60549 Frankfurt am Main, Nemčija. e-pošta: medinfo_de@eisai.net. Tel: + 49 (0) 69 66 58 50. **Opozorilo:** Pred predpisovanjem preberite celoten povzetek glavnih značilnosti zdravila. **Datum priprave informacije:** 9/2025.

Eisai Biogen

Samo za strokovno javnost. I Datum priprave: april 2026 I EP-LECA-26-00010 I Biogen-285601

Podrobnejše informacije so na voljo pri: Eisai GmbH, Edmund-Rumpler-Straße 3, 60549 Frankfurt am Main, Nemčija. e-pošta: medinfo_de@eisai.net. Tel: + 49 (0) 69 66 58 50
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