Comparative Health Economic Evaluation of Alzheimer's Diagnostic-Treatment Strategies in the Era of Amyloid-Targeting Therapies: A Conceptual Model Framework

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INTRODUCTION

- Amyloid-targeting therapies (ATTs), such as lecanemab and donanemab, represent a paradigm shift in the treatment of Alzheimer's disease (AD).
- Initiation of ATTs requires confirmed β-amyloid pathology, as these agents specifically target and remove amyloid plaques. Without such confirmation, treatment is not clinically justified and is unlikely to provide benefit.
- Additionally, β-amyloid positron emission tomography (PET) imaging is required to monitor treatment response and guide treatment discontinuation decisions[1].
- The most recent diagnostic modalities comprise a combination of techniques targeting specific biomarkers, including β-amyloid PET, cerebrospinal fluid (CSF) biomarkers such as Aβ1-42, t-tau, p-tau181, and emerging blood-based biomarkers (BBBs) such as p-tau181, p-tau217, and p-tau231.
- The economic consequences of selecting a diagnostic strategy to guide treatment decisions remain relatively underexplored, largely because ATTs have only recently received regulatory approval.

OBJECTIVE

- To conceptualize a health economic model evaluating the diagnostic accuracy, downstream clinical outcomes, cost-effectiveness, and budget impact of **diagnostic-treatment combinations** involving ^{18}F-flutemetamol PET (visual or with quantification), CSF testing, and BBBs in patients with mild cognitive impairment (MCI) or suspected AD.

METHODS

- A Markov cohort model was developed to simulate diagnostic and treatment pathways **(Figure 1)** for individuals aged 40–79 years with MCI or suspected AD over a lifetime horizon.
- Key model components include:
  - Health states: MCI±AD, mild AD, moderate AD, severe AD, other dementia, and death **(Figure 2)**.
  - Diagnostic accuracy inputs: Sensitivity and specificity used to determine diagnostic accuracy and guide downstream treatment allocation.
  - Treatment strategies: Three arms were considered – symptomatic care, lecanemab, and donanemab.
  - Diagnostic modalities evaluated:

i. β-amyloid PET with visual assessment

ii. β-amyloid PET with quantification

iii. CSF testing

Patients with inconclusive results are referred for β-amyloid PET imaging for further evaluation.

iv. BBBs*:

The BBBs were evaluated under two scenarios:

a) Scenario 1 (aligned with intended use): BBBs are used as a screening tool, primarily to exclude individuals without evidence of β-amyloid pathology. Patients with high and indeterminate likelihood of amyloid presence are subsequently referred for confirmatory testing.

b) Scenario 2 (alternative clinical use): BBBs are employed as both a screening and a prescribing tool, enabling treatment initiation in patients who test positive with a high likelihood of β-amyloid pathology, without the need for a confirmatory test. Only patients with indeterminate results are referred for additional tests to confirm diagnosis.

  - Treatment discontinuation was modelled according to:

i. Donanemab: two PET scans were considered (12 and 24 months) to evaluate treatment efficacy; >75% discontinued at 18 months[3].

ii. Lecanemab: assumed that patients remain on treatment until disease progression to moderate or severe dementia.

- Transition probabilities were informed by the published literature and were stratified by treatment allocation. For states beyond the scope of ATTs (e.g., moderate/severe AD), progression followed the symptomatic care trajectory (reflecting a combination of conventional therapies, e.g., AChE inhibitors, memantine, and vascular modifiers). Health state-specific costs and utilities were applied across all health states.
- BBB accuracy and cut-off thresholds vary across publications. Therefore, the analysis was conducted using two validation cohorts (Lumipulse 510K and Mayo Clinic), each with cohort-specific cutoffs[2,4].
- Model outcomes include misdiagnosis rates (false positives and false negatives), resources used, and quality of life for correctly and incorrectly diagnosed patients, incorporated to estimate economic impact.
- The model also includes a budget impact component to assess the financial implications of each diagnostic-treatment strategy from the payer perspective.

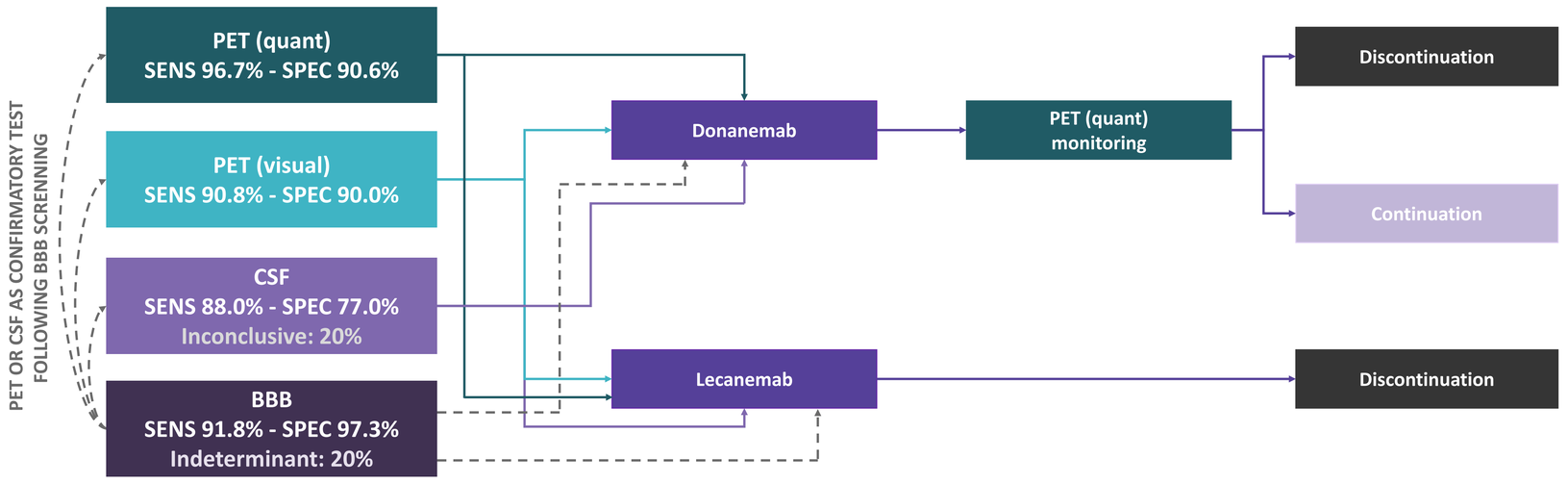

Figure 1. Simplified simulated diagnostic and treatment pathways.

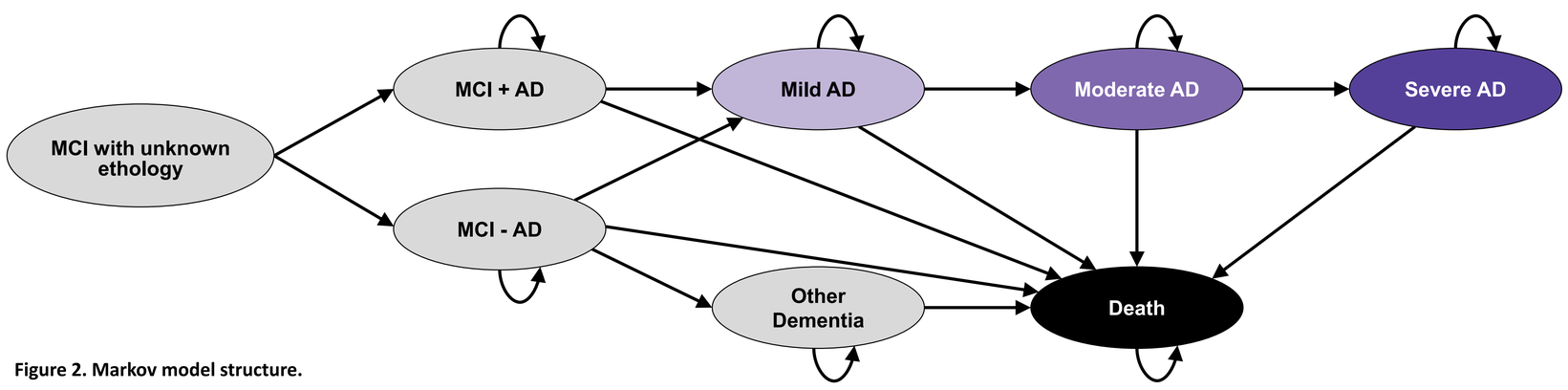

Figure 2. Markov model structure.

RESULTS

- The model concept allows for full economic evaluation of the integrated diagnostic-treatment pathway.
- The modelled diagnostic accuracy accounts for the proportion of inconclusive results associated with each modality, ensuring a more realistic and comprehensive assessment:
  - β-amyloid PET with quantification: **93.93%** correctly diagnosed patients
  - β-amyloid PET without quantification: **90.44%** correctly diagnosed patients
  - CSF testing **followed by a confirmatory PET test**: **85.19%** correctly diagnosed patients
  - BBB as a screening tool **followed by a confirmatory PET test** (Scenario 1): **94.06%** correctly diagnosed patients
- Among these, ^{18}F-flutemetamol PET with quantification demonstrated very high diagnostic accuracy, driven by its high reported combined sensitivity and specificity. **^{18}F-flutemetamol PET with quantification also reduces costs and resource use by eliminating the need for additional confirmatory tests to establish β-amyloid pathology**.
- Visual vs. quantitative β-amyloid PET interpretation is reported to have ~7.5% discordance in the clinical setting (IDEAS study), with implications for misdiagnosis-related treatment cost and for patients[5].
- Model outcomes demonstrate that even small differences in diagnostic accuracy can lead to amplified effects on treatment allocation, long-term outcomes, and overall cost-effectiveness and budget impact.

CONCLUSIONS

To our knowledge, this is the first economic model to jointly assess different diagnostic modalities followed by subsequent treatment pathways in AD, capturing the clinical and economic implications of linking diagnosis to therapy.

Incorporating β-amyloid quantification via ^{18}F-flutemetamol PET improves diagnostic precision and enables treatment monitoring. Neither CSF nor BBB alone currently supports these characteristics; therefore, β-amyloid quantification via ^{18}F-flutemetamol PET may help reduce unnecessary treatment and risk exposure, and improve resource allocation.

Quantitative PET, when paired with ATTs, stopping rules, and monitoring protocols, offers strong potential for improving diagnostic precision and optimizing resource use and its allocation.

Findings are relevant to payer decision-making and support optimization of diagnostic and therapeutic pathways in the context of ATTs, highlighting the importance of jointly assessing diagnostic accuracy and treatment effectiveness to enable more informed decisions and provide a comprehensive comparison of currently available diagnostic modalities.

* In May 2025, the U.S. Food and Drug Administration cleared the first BBB test to support AD diagnosis; however, it is not approved for screening or standalone use and requires confirmatory testing[2].

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Abbreviations: AChE = Acetylcholinesterase; AD = Alzheimer's disease; ATTs = Amyloid targeting therapies; BBB = blood-based biomarker; CSF = cerebrospinal fluid; MCI = mild cognitive impairment; PET = positron emission tomography; quant = quantification; SENS = sensitivity; SPEC = specificity.

References: 1. Rabinovici G., et al., Donanemab: Appropriate use recommendations, The Journal of Prevention of Alzheimer's Disease. 2025, 12(5); 2. Department of Health and Human Services. FDA. Approval decision of Lumipulse G pTau217 /P-Amyloid 1-42 Plasma Ratio. OMB. No. 0910-0120. May 2025; 3.Mintun M., Donanemab in Early Symptomatic Alzheimer's Disease: Efficacy and Safety from the TRAILBLAZER-ALZ 2 Long-Term Extension. Eli Lilly and Company, Indianapolis, IN. AAIC 2025; 4. Piura Y., et al., Diagnostic performance of plasma p-tau217 and Aβ42/40 biomarkers in the outpatient memory clinic, Alzheimer's Dement. 2025, 21: e70316; 5. IDEAS presentation at AAIC 2022.