Cost-effectiveness of Alzheimer's disease CSF biomarkers and amyloid-PET in early-onset cognitive impairment diagnosis.

Jose Contador[a*], Ana Magdalena Vargas-Martínez[b*], Raquel Sánchez-Valle[a], Marta Trapero-Bertran[b], Albert Lladó[a†]

a. Alzheimer's Disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic de Barcelona. Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS). Univerity of Barcelona. Barcelona, Spain.
b. Departament de Cienciès Bàsiques, Universitat Internacional de Catalunya, Barcelona, Spain

*These authors contributed equally to this work.

†Corresponding author: Dr Albert. Lladó MD, PhD, Alzheimer 's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic Barcelona. Carrer Villarroel 170, 08036 Barcelona, Spain. Tel.: +34 932275785; fax: +34 932275783; e-mail: allado@clinic.cat

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Abstract

BACKGROUND: To determine the cost-effectiveness of amyloid-positron emission tomography (PET) compared to Alzheimer's disease (AD) cerebrospinal fluid (CSF) biomarkers (amyloid-β_{42}, total-Tau and phosphorylated-Tau) for the diagnosis of AD in patients with early-onset cognitive impairment.

METHODS: A decision tree model using a national health care perspective was developed to compare the costs and effectiveness associated with Amyloid-PET and AD CSF biomarkers. Available evidence from the literature and primary data from Hospital Clínic de Barcelona were used to inform the model and calculate the efficiency of these diagnostic alternatives. Medical visits and diagnostic procedures were considered and reported in €2020. We calculated the incremental cost-effectiveness ratio to measure the cost per % of correct diagnoses detected and we perform one-way deterministic and probabilistic sensitivity analyses to assess the uncertainty of these results.

RESULTS: Compared with AD CSF biomarkers, Amyloid-PET resulted in 7.40 % more correctly diagnosed cases of AD, with an incremental total mean cost of 146,854.80€ per 100 cases. We found a 50% of probability that Amyloid-PET was cost-effective for a willingness to pay (WTP) of €19,840.39 per corrected case detected. Using a WTP of €75,000, the probability that it is cost-effective reached a maximum of 76.9%.

CONCLUSIONS: Amyloid-PET is not a cost-effective technique compared to AD CSF biomarkers, unless the funder is willing to pay a minimum of €19,840.39 to detect one correct case more. Furthermore, obtaining CSF provides simultaneous information on amyloid β and tau biomarkers and allows other biomarkers to be analyzed at a relatively low cost.

Keywords: Alzheimer's disease, cost-effectiveness, cerebrospinal fluid biomarkers, amyloid-positron emission tomography, early diagnosis

Introduction

Worldwide, fifty-five million people are estimated to live with dementia, representing the 7th leading cause of mortality globally and a high cost to society. Although the dementia costs are hampered by different bias, the global cost of dementia was estimated to be 1.3 trillion US$ in 2019[1]. Alzheimer's disease (AD) is the leading cause of neurodegenerative dementias and made up about 60% of cases of dementia. With a growing incidence and prevalence in the last years due to the aging, AD is a global epidemic with no yet effective treatment and representing a huge burden for families, health-care systems and even the entire society to care and support patients.

AD is characterized by a progressive cognitive decline due to the accumulation of extracellular β-amyloid plaques and intracellular neurofibrillary tangles (NFT) of hyperphosphorylated tau proteins, together with neuronal death and brain atrophy[2]. Early-onset Alzheimer's disease (EOAD, age at onset <65 years), overshadowed by the more common late-onset AD (>65 years), continues being the most frequent neurodegenerative dementia in young patients and represents about 5% of AD[3]. Both entities feature the same neuropathological hallmarks. However, EOAD, less influenced by aging processes, is associated with specific clinical and neurobiological characteristics, delays in diagnosis and age-related psychosocial needs[4].

Nowadays, the underlying neuropathological processes in AD can be evaluated *in vivo* through biofluids (e.g., cerebrospinal fluid (CSF)) or neuroimaging techniques (e.g., Positron Emission Tomography (PET)), allowing a diagnosis of cognitive impairment due to AD. These biomarkers were already included in the National Institute on Aging and Alzheimer's Association (NIA-AA) diagnostic criteria 2011[5, 6] and shifted from a classification based on clinical and pathological findings to a biological definition of the disease in the Research Framework 2018[7]. In the last, biomarkers are divided into biomarkers of β-amyloid plaques (A), biomarkers of fibrillary tau (T) and biomarkers of neurodegeneration (N). These biomarkers also offer the opportunity to identify subjects in preclinical stages and with mild cognitive impairment at risk of evolution to AD dementia, in which potential disease-modifying treatment might

slow or stop the progression of the disease before neurodegeneration has exerted its effects. In addition, previous analyses without including AD biomarkers have suggested that an early detection of AD patients and the subsequent pharmacological/non-pharmacological interventions generate cost savings[8]. The evolution of the underlying pathology cannot be stopped nowadays, however, a more specific diagnosis may help physicians to guide available therapy and to properly advise patients and caregivers.

Increased accessibility to biomarkers, as any other health intervention, should be evaluated in terms of cost-effectiveness to allow well-informed decisions to be made about care planning in qualified memory clinics [9]. Previous evidence suggests that amyloid-PET[10–12] or CSF AD biomarkers[13–15] are cost-effective diagnostic strategies for the diagnosis/prognosis of AD cognitive impairment compared to clinical criteria, including studies with heterogenous health-care resources, sensitivity/specificity data, AD populations (i.e. MCI or dementia) or outcomes and time horizons. Nevertheless, the cost-effectiveness has not been evaluated for the diagnosis of AD among early-onset cognitive impairment, and whether there are cost-effectiveness gains or savings comparing PET scans versus CSF tests remains unanswered[16].

Here, we aimed to evaluate the cost-effectiveness of the use of Amyloid-PET (A biomarker) versus lumbar puncture (LP) and the analysis of CSF amyloid-β_{42} ($A\beta_{42}$), phosphorylated-Tau (p-Tau) and total-Tau (t-Tau) (ATN biomarkers) for the correct diagnosis of AD among patients with early-onset cognitive impairment in a tertiary hospital. Our study may help to dictate the indication for amyloid-PET or CSF analysis in clinical practice and determine the healthcare policy in AD.

Methods

AD in an early-onset Memory clinic

First, to calculate the prevalence of EOAD in a University Hospital-Memory clinic setting, we retrospectively reviewed all the early-onset dementia diagnoses during 2016-2019 in the Alzheimer's disease and Other Cognitive Disorders Unit, Hospital Clínic de Barcelona, Barcelona, Spain. We reviewed clinical charts from subjects aged <65 years who were referred to a tertiary hospital due to early-

onset cognitive complaints and were diagnosed with an early onset dementia (n=189, 48.1% females). In this period, 52 patients (51.9% females) were diagnosed with EOAD according to NIA-AA 2011 criteria, resulting in a prevalence of 27.51%.

On the other hand, to obtain the percentage of patients in whom a LP is not performed due to technical difficulties or consent withdraw, we divided the number of patients in whom this procedure was not possible (n=12) by the total of LPs indicated in our center during the same period (n=144).

This study was approved by Hospital Clínic de Barcelona Ethics Committee and all the individuals gave written informed consent for their clinical data to be used for research purposes.

Model description

An economic evaluation was performed by means of cost-effectiveness analysis comparing two available diagnostic alternatives for AD: the determination of AD CSF biomarkers ($A\beta_{42}$, t-Tau and p-Tau) and Amyloid-PET. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) have been applied to evaluate this investigation [17].

A decision tree model was developed to synthesize the identified evidence and estimate the costs and effectiveness associated with each diagnostic strategy for a cohort of 100 patients. The fundamental concepts of this diagnosis-based analysis were adapted from Rautenberg et al. (2020)[18]. Figure 1 shows a schematic outline of the test-based modelling approach.

This decision tree shows intermediate outcomes such as true positive (TP), false positive (FP), true negative (TN) and false negative (FN), which are the direct result of doing the diagnostic test only. At the beginning of the model the patients are tested with AD CSF biomarkers or Amyloid-PET. In both arms of the model, these tests can be positive or negative according to the threshold in each diagnostic test. A positive test (T+) could be TP corresponding with the positive predictive value (PPV) or FP. Likewise, a negative test (T-) could be TN corresponding with the positive predictive value (NPV) or FN.

The effectiveness measure was “% of cases appropriate or correctly diagnosed”, which refers to “True positive as AD” and “True negative as not AD”. A time horizon of 3 months was adopted (time to diagnosis), and therefore additional costs and outcomes were not discounted. To measure the cost per % of correct diagnoses detected, we calculated the incremental cost-effectiveness ratio (ICER): difference in cost between the two strategies divided by the difference in their effects.

Model inputs

Several sources of evidence, combining published literature[18–20] and primary data from Hospital Clinic de Barcelona, were used to inform the model. The input data were: EOAD prevalence (Hospital Clinic de Barcelona), sensitivity and specificity of AD biomarkers in CSF and sensitivity and specificity of Amyloid-PET. Sensitivity and specificity data were selected from published data in studies with a confirmed neuropathological diagnosis of AD[19, 20]. Table 1 shows the values and information sources of the most important probabilities used in the base case.

The PPV and NPV of each diagnostic strategy were calculated using the data related to prevalence, sensitivity and specificity (Table S1, S2a, S2b and S3 in Supplementary material for more details about their calculation) according to Rautenberg et al.[18]. A cohort of 100 patients was used to construct these tables. Table S3 (Supplementary material) shows the calculation of the PPV and NPV, as well as the proportion of patients that T+, which is needed for the model.

Model outcomes and clinical effectiveness

Effectiveness of diagnostic tests was measured in natural clinical units in terms of % of AD cases correctly diagnosed. Therefore, the effectiveness in each arm of the model is directly related to the sensitivity and specificity of each diagnostic strategy, that is, TP and TN of each alternative compared, whose values have been previously calculated.

Resource use and unit costs

Given the national health care perspective adopted for the analysis, only direct healthcare costs (medical visits and diagnostic procedures) were included. Costs were measured in euros (€2020). The costs related to the analysis of AD biomarkers in CSF (Lumipulse G®, Fujirebio) or Amyloid-PET (flutemetamol or florbetaben) were reported by authors using data from Hospital Clinic de Barcelona in 2020 (536.78€ and 2,170€, respectively). The cost of patient who did not undergo LP due to technical difficulties or patient's consent withdraw, was calculated as the cost of LP (subtracting the cost of kits for biochemical analyses) plus amyloid-PET cost (€350.78 + 2,170€). Similarly, the costs data related to a first outpatient visit plus two subsequent outpatient visits, which are considered necessary to conclude a diagnosis in both interventions, were also reported by authors (218.68€).

Sensitivity analysis

We analyzed the uncertainty around model inputs. One-way deterministic and probabilistic sensitivity analyses were performed. When no uncertainty boundaries were obtained for the input estimates included in the model, the analysis adopted standard methods for defining uncertainty and default input values were varied by 10% (Table 2).

The results of the deterministic sensitivity analysis were presented using a tornado plot, which illustrates the impact of each parameter change as the difference that it has on the ICER calculation compared with the base case. In addition, probabilistic sensitivity analysis was shown using the incremental cost-effectiveness plane. It was performed using 1,000 Monte Carlo simulations. Distributional assumptions were made according to recommended guidelines[21]. Probabilities were characterized by beta distributions and costs by gamma distributions. Incremental cost-effectiveness plane was used to represent this uncertainty. Different willingness to pay (WTP) has been considered in order to measure the cost-effectiveness probability of Amyloid-PET compared to AD CSF biomarkers.

Results

Base case results

For a cohort of 100 patients, the use of Amyloid-PET compared with AD CSF biomarkers resulted in 7.40 % more cases of AD correctly diagnosed. In addition, the use of Amyloid-PET for AD diagnosis represented an incremental total mean cost compared to AD CSF biomarkers of 146,854.80€. Thus, the base case results revealed for this population group that Amyloid-PET is more effective but also more expensive (Table 3). Therefore, the amyloid-PET would be efficient or cost-effective if there is a willingness to pay of €19,840.39 for one additional case.

Sensitivity analysis

The results of the deterministic sensitivity analysis are shown in Table 4. The use of amyloid-PET was slightly more effective but also much more expensive than the use of AD CSF biomarkers when sensitivity and specificity values of AD CSF biomarkers and Amyloid-PET were used and costs of both interventions and prevalence of EOAD were raised up and down to maximum and minimum values obtained from available evidence.

The tornado diagram in Figure 2 indicates that the specificity of AD CSF biomarkers and Amyloid-PET is the parameter that has the greatest impact on the diagnostic strategy cost-effectiveness.

Table 5 shows the findings of the probabilistic sensitivity analysis. The uncertainty around the ratio is still wide with an ICER of 22,340.93€ per one correctly diagnosed case more a 95% confidence interval of 26,353.39€. For a WTP threshold of €10,000, the Amyloid-PET has 22% of probability of being cost-effective and 18% of probability of being dominated (less effective and more costly) compared to AD CSF biomarkers.

The incremental cost-effectiveness plane is shown in Figure 3a, which represents the average ICER and the difference in cost and difference on effectiveness obtained for all simulations. The scattering in this figure shows quite high uncertainty in terms of the benefit that the Amyloid-PET has to diagnose correct cases. Furthermore, the acceptability curve is shown in Figure 3b, which represents the probability for Amyloid-PET of being a cost-effective intervention taking in account different WTP per case correctly detected. This curve shows that the average probability of Amyloid-PET being cost-effective starts rising

around a WTP per case correctly detected of approximately €5,000. This technology reaches a 50% of probability of being cost-effective only from a WTP of €19,840 per case correctly detected. Using a WTP of € 75,000, the probability of being cost-effective reaches a maximum of 76.9%. Unless the funder is willing to pay this amount of money to detect one more correct case, this technology would not be cost-effective.

Discussion

In this study, we evaluate the cost-effectiveness of the use of Amyloid-PET versus AD CSF biomarkers for AD diagnosis in patients with early-onset cognitive impairment. We found a 50% of probability that Amyloid-PET was cost-effective only from a WTP of €19,840 per case correctly detected. In addition, with a WTP of € 75,000, the probability that it is cost-effective reaches a maximum of 76.9%. So, unless the funder is willing to pay this amount of money to detect one correct case more, Amyloid-PET would not be cost-effective.

Over the past 10-20 years, there has been remarkable progress in the development and availability of *in-vivo* AD biomarkers and in their applications in clinical practice. An accurate and early AD diagnosis is a clinical challenge and is crucial for an individualized intervention and a more accurate prognosis, as well as advice and information to patients and their families. Furthermore, the diagnosis could have different implications in EOAD than in late-onset cases, since EOAD could have greater personal, family, labor, social and economic impact. The two most established biomarkers capable of detecting AD pathology are AD CSF biomarkers and Amyloid-PET. The former is the only one that allows detecting both main AD hallmarks (neuritic plaques and NFT) and complete the entire ATN profile in a single test, but require the extraction of CSF through a LP, an intervention that might be negatively perceived by the patient when is not well informed about the available safety evidence[22]. However, some studies have shown that the degree of discomfort is not greater in a LP than in a magnetic resonance imaging scan[23]. On the other hand, Amyloid-PET is minimally invasive by injecting radioactive material, although it only allows the detection of cerebral amyloid deposits and is more expensive.

There are few studies focused on the cost-effectiveness of different AD biomarkers for the diagnosis of AD. However, cost-effectiveness of both AD CSF biomarkers and amyloid-PET compared to clinical criteria has been previously described[10–14]. The use of $A\beta_{42}$, t-tau and p-tau proteins tests in CSF is clearly cost-effective in MCI patients compared to a clinical diagnosis but might be not conclusive in dementia patients[15], possibly due to some limitations of the study, like the quality of the specificity and sensitivity of the clinical criteria for AD diagnosis. Also, the different study populations, the variations in the progression of the disease in each one or the inclusion of off-label treatments for MCI (cholinesterase inhibitors)[24] in the cost are conditions that could impact outcomes in previous studies. On the other hand, Amyloid-PET also has demonstrated its impact on the diagnostic confidence of AD and its cost-effectiveness, including health outcomes[25, 26].

Here, we focused on comparing the cost-effectiveness of the two main approaches for AD diagnosis in a tertiary hospital, without considering other variables such as non-pharmacological or pharmacological treatments. In this context we have developed an economic evaluation that, considering published and own data, compares these two alternatives for the detection of AD in early-onset cognitive impairment. Different factors have an impact in our cost-effectiveness study: EOAD prevalence, sensibility and specificity of AD CSF biomarkers and Amyloid-PET and their costs. We have used own data from 2016-2019 to obtain the EOAD prevalence in our early-onset dementia outpatient clinic. We described an EOAD prevalence of approximately 30% in patients with early-onset cognitive impairment referred to our clinic. This prevalence could vary between different centers, but it is probably generalizable to most tertiary centers.

As the tornado diagram indicates, specificity of both analyzed biomarkers is the variable that could have the greatest impact on the cost-effectiveness of the diagnostic strategy. Specificity is difficult to be established in a specific cohort as they require neuropathological confirmation. So, we decided to use published data that shown sensitivity and specificity of these biomarkers in cases with a pathological diagnosis. Different studies have showed a significant relationship between neuropathological changes of AD in the brain (neuritic plaques and NFT)

and the levels of AD CSF biomarkers or Amyloid-PET[19, 20], although these studies have mainly analyzed these relationships in patients with an advance stage of dementia and included few patients with early-onset dementia. Tapiola et al. (2009) have shown that the ratio p-tau/$A\beta_{42}$ had a sensitivity of 91.6% and a specificity of 85.7% to detect AD pathology. However, this sensitivity and specificity could be even higher in early-onset patients[27] or analyzing the combination of $A\beta_{42}$ with $A\beta_{40}$, which could increase the agreement between CSF biomarkers and Amyloid-PET[28]. Therefore, the introduction of new CSF biomarkers or new techniques with higher sensitivity/specificity could improve the diagnostic capacity of AD CSF biomarkers without significantly increasing their cost. We also found a relatively high percentage (8.3%) of patient in whom the LP was not performed due to technical difficulties or patient's consent withdraw. Therefore, a good selection of patients and informing and reassuring patients about the procedure and its importance before LP indication could decrease the cost of CSF biomarkers[22]. Other advantages of obtaining CSF through of a LP is to allow analyzing other biomarkers such as α-synuclein, 14-3-3 protein or neurofilament light chain, which could be very useful to complete the diagnostic study if AD CSF biomarkers are negative. In this way, it has recently been described that α-synuclein Real-Time QUaking-Induced Conversion (RT-QuIC) provides an accurate marker of synucleinopathies linked to Lewy body pathology and may have a role in the early diagnosis of patients with cognitive impairment[29, 30]. In spite of all this, if LP is contraindicated, Amyloid-PET continues being a good alternative to establish an AD diagnosis.

A recent review about Amyloid-PET imaging in AD has described, analyzing different amyloid tracers ([11C]PiB, [18F]Florbetapir, [18F]flutemetamol, [18F]florbetaben), a sensitivity between 91–97.9% and a specificity between 90–100% to detect AD-related neuropathology[20]. We used these data in our analyses, although again, these high rates of sensitivity and specificity in detecting amyloid pathology is mainly evaluated in individuals with an advanced dementia and a short life expectancy, and these variables could lightly change their sensitivity and specificity in early stages. As the different AD clinical phenotypes could also be seen in other neurodegenerative diseases, it has been suggested that the positivity of both, amyloid and tau biomarkers, is necessary to

increase the likelihood of AD as the primary diagnosis[31]. In the future, if tau-PET is widely use in the clinical practice, the cost to demonstrate the positivity of amyloid β and tau pathology through PET will significantly increase the cost of AD diagnosis, and discrepancies between the two PET tracers may appear that decrease the sensitivity and specificity for the diagnosis of AD[32].

The main limitation of this study is that all factors that have an impact in the cost-effectiveness results could vary between centers (AD prevalence, costs of testing, sensibility and specificity of CSF biomarkers and amyloid-PET and the interaction of these variables). Despite that, the combination of own and published data makes that the overall conclusion is likely extrapolated to majority of tertiary centers. Another limitation is the 3-month time horizon that we adopted, which only evaluates the time to diagnosis, but not the derived costs and differences in health outcomes for true positive and negative diagnoses, and therefore we cannot calculate the cost per quality-adjusted life-years (QALYs). In addition to pharmacological and non-pharmacological interventions, there are medical consequences that are linked to each outcome that we are not evaluating: less overtreatment in FP, less undertreatment in FN, and corresponding treatment side-effects or benefits forgone. Also, a full test pathway, including non-medical effects of testing on patient outcomes, is not considered. Ruling out AD or a false AD diagnosis may have important emotional, decision-making and future care planning reactions that contribute to the accuracy of the cost-effectiveness [33]. On the other hand, our approach allowed us to make a study comparing the two main diagnostic tests for AD and avoid greater uncertainties. The preferences of the patients were not included in the analysis. Lumbar puncture is usually well-tolerated, but some patients might prefer a neuroimaging procedure to the LP. Further studies comparing cost-effectiveness of AD biomarkers between early- and late-onset presentations are also needed and, even if the number of women and men with EOAD was quite similar in our cohort in line with a recent meta-analysis[34], sex-differences in cost-effectiveness might have implications for clinical practice. However, these aims are beyond the scope of our work, which focuses on investigating the cost-effectiveness of biomarkers for AD diagnosis among patients with early-onset cognitive impairment in a memory-clinic setting

In conclusion, we found that Amyloid-PET does not reach the 50% of probability of being cost-effective compared to AD CSF biomarkers (lumbar puncture), unless the funder is willing to pay €19.840. It is also worth considering that CSF biomarkers provide simultaneous information on the two types of AD biomarkers (amyloid β and tau). Furthermore, obtaining CSF makes it possible to analyze other biomarkers at a relatively low cost, which could be very useful in the differential diagnosis of patients with cognitive impairment. Future cost-effectiveness studies analyzing the use of different biomarkers for the diagnosis of EOAD with a longer time horizon are needed to calculate the QALYs for each biomarker.

Declarations

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References

1. World Health Organization (2021) Public health response to dementia

2. Jack CR, Holtzman DM (2013) Biomarker modeling of alzheimer's disease. Neuron 80:1347–1358. https://doi.org/10.1016/j.neuron.2013.12.003

3. Zhu XC, Tan L, Wang HF, et al (2015) Rate of early onset Alzheimer's disease: A systematic review and meta-analysis. Ann. Transl. Med. 3

4. Mendez MF, Lee AS, Joshi A, Shapira JS (2012) Nonamnestic presentations of early-onset Alzheimer's disease. Am J Alzheimers Dis Other Demen 27:413–420. https://doi.org/10.1177/1533317512454711

5. McKhann GM, Knopman DS, Chertkow H, et al (2011) The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement 7:263–269. https://doi.org/10.1016/j.jalz.2011.03.005

6. Albert MS, DeKosky ST, Dickson D, et al (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement 7:270–279. https://doi.org/10.1016/j.jalz.2011.03.008

7. Jack CR, Bennett DA, Blennow K, et al (2018) NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's Dement 14:535–562. https://doi.org/10.1016/j.jalz.2018.02.018

8. Weimer DL, Sager MA (2009) Early identification and treatment of Alzheimer's disease: Social and fiscal outcomes. Alzheimer's Dement 5:215–226. https://doi.org/10.1016/j.jalz.2009.01.028

9. Frisoni GB, Boccardi M, Barkhof F, et al (2017) Strategic roadmap for an early diagnosis of Alzheimer's disease based on biomarkers. Lancet Neurol 16:661–676. https://doi.org/10.1016/S1474-4422(17)30159-X

10. Lee YS, Youn HC, Jeong HG, et al (2021) Cost-effectiveness of using amyloid positron emission tomography in individuals with mild cognitive impairment. Cost Eff Resour Alloc 19:1–10. https://doi.org/10.1186/s12962-021-00300-9

11. Hornberger J, Michalopoulos S, Dai M, et al (2015) Cost-Effectiveness of Florbetapir-PET in Alzheimer's Disease: A Spanish Societal Perspective. J Ment Health Policy Econ 18:63–73

12. Guo S, Getsios D, Hernandez L, et al (2012) Florbetaben PET in the Early Diagnosis of Alzheimer ' s Disease : A Discrete Event Simulation to Explore Its Potential Value and Key Data Gaps. 2012:.

https://doi.org/10.1155/2012/548157

13. Lee SAW, Sposato LA, Hachinski V, Cipriano LE (2017) Cost-effectiveness of cerebrospinal biomarkers for the diagnosis of Alzheimer's disease. Alzheimer's Res Ther 9:1–14. https://doi.org/10.1186/s13195-017-0243-0

14. Handels RLH, Wimo A, Dodel R, et al (2017) Cost-Utility of Using Alzheimer's Disease Biomarkers in Cerebrospinal Fluid to Predict Progression from Mild Cognitive Impairment to Dementia. J Alzheimer's Dis 60:1477–1487. https://doi.org/10.3233/JAD-170324

15. Valcárcel-Nazco C, Perestelo-Pérez L, Molinuevo JL, et al (2014) Cost-effectiveness of the use of biomarkers in cerebrospinal fluid for Alzheimer's disease. J Alzheimer's Dis 42:777–788. https://doi.org/10.3233/JAD-132216

16. Wittenberg R, Knapp M, Karagiannidou M, et al (2019) Economic impacts of introducing diagnostics for mild cognitive impairment Alzheimer's disease patients. Alzheimer's Dement Transl Res Clin Interv 5:382–387. https://doi.org/10.1016/j.trci.2019.06.001

17. Husereau D, Drummond M, Augustovski F, et al (2022) Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. BJOG 129:336–344. https://doi.org/10.1111/1471-0528.17012

18. Rautenberg T, Gerritsen A, Downes M (2020) Health economic decision tree models of diagnostics for dummies: A pictorial primer. Diagnostics 10:. https://doi.org/10.3390/diagnostics10030158

19. Tapiola T, Alafuzoff I, Herukka SK, et al (2009) Cerebrospinal fluid β-amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain. Arch Neurol 66:382–389. https://doi.org/10.1001/archneurol.2008.596

20. Chandra A, Valkimadi PE, Pagano G, et al (2019) Applications of amyloid,

tau, and neuroinflammation PET imaging to Alzheimer's disease and mild cognitive impairment. Hum Brain Mapp 40:5424–5442. https://doi.org/10.1002/hbm.24782

21. Briggs A, Claxton K, Sculpher M (2006) Decision modelling for health economic evaluation. Oxford University Press, United Kingdom

22. Hampel H, Lleó A, Ikeuchi T, et al (2021) State-of-the-art of lumbar puncture and its place in the journey of patients with Alzheimer ' s disease. 1–19. https://doi.org/10.1002/alz.12372

23. Falgàs N, Tort-Merino A, Balasa M, et al (2019) Clinical applicability of diagnostic biomarkers in early-onset cognitive impairment. Eur J Neurol 26:1098–1104. https://doi.org/10.1111/ene.13945

24. Russ TC, Morling JR (2012) Cholinesterase inhibitors for mild cognitive impairment. Cochrane database Syst Rev 2012:CD009132. https://doi.org/10.1002/14651858.CD009132.pub2

25. Boccardi M, Altomare D, Ferrari C, et al (2016) Assessment of the incremental diagnostic value of florbetapir F 18 imaging in patients with cognitive impairment: The incremental diagnostic value of amyloid PET with [18F]-florbetapir (INDIA-FBP) study. JAMA Neurol 73:1417–1424. https://doi.org/10.1001/jamaneurol.2016.3751

26. Hornberger J, Bae J, Watson I, et al (2017) Clinical and cost implications of amyloid beta detection with amyloid beta positron emission tomography imaging in early Alzheimer's disease–the case of florbetapir. Curr Med Res Opin 33:675–685. https://doi.org/10.1080/03007995.2016.1277197

27. Bouwman FH, Schoonenboom NSM, Verwey NA, et al (2009) CSF biomarker levels in early and late onset Alzheimer's disease. Neurobiol Aging 30:1895–1901. https://doi.org/10.1016/j.neurobiolaging.2008.02.007

28. Alcolea D, Pegueroles J, Muñoz L, et al (2019) Agreement of amyloid PET and CSF biomarkers for Alzheimer's disease on Lumipulse. Ann Clin

Transl Neurol 6:1815–1824. https://doi.org/10.1002/acn3.50873

29. Bongianni M, Ladogana A, Capaldi S, et al (2019) α-Synuclein RT-QuIC assay in cerebrospinal fluid of patients with dementia with Lewy bodies. Ann Clin Transl Neurol 6:2120–2126. https://doi.org/10.1002/acn3.50897

30. Rossi M, Candelise N, Baiardi S, et al (2020) Ultrasensitive RT-QuIC assay with high sensitivity and specificity for Lewy body-associated synucleinopathies. Acta Neuropathol 140:49–62. https://doi.org/10.1007/s00401-020-02160-8

31. Dubois B, Villain N, Frisoni GB, et al (2021) Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. Lancet Neurol 20:484–496. https://doi.org/10.1016/S1474-4422(21)00066-1

32. Bischof GN, Dodich A, Boccardi M, et al (2021) Clinical validity of second-generation tau PET tracers as biomarkers for Alzheimer's disease in the context of a structured 5-phase development framework. Eur J Nucl Med Mol Imaging 48:2110–2120. https://doi.org/10.1007/s00259-020-05156-4

33. Bossuyt PMM, McCaffery K (2009) Additional patient outcomes and pathways in evaluations of testing. Med Decis Mak 29:30–38. https://doi.org/10.1177/0272989X09347013

34. Hendriks S, Peetoom K, Bakker C, et al (2021) Global Prevalence of Young-Onset Dementia. JAMA Neurol 78:1080. https://doi.org/10.1001/jamaneurol.2021.2161

Figure captions:

Fig. 1 Structure of the decision-analytic model of the test-based approach to diagnostic modelling. Key: AD+: Alzheimer's disease positive; AD-: Alzheimer's disease negative; All T+: All test positives; All T+': complement of all test positives

which is 1-All T+; Amyloid-PET: amyloid-positron emission tomography; FN: false negative; FP: false positive; LP: Lumbar puncture; NPV: Negative predictive value; NPV': complement of negative predictive value which is 1-NPV; PPV: Positive predictive value; PPV': complement of positive predictive value which is 1-PPV; T+: test positive; T-: test negative; TN: true negative; TP: true positive

Fig. 2 Change in the incremental cost-effectiveness ratio in euros 2020 in the univariate sensitivity analysis. Key: AD, Alzheimer's disease, LP, lumbar puncture; Amyloid-PET: amyloid-positron emission tomography

Fig. 3 a) Incremental cost-effectiveness plane by correct diagnosis and b) Acceptability curve of Amyloid-PET

Figure 1

Click here to access/download;Figure;Fig1.jpg

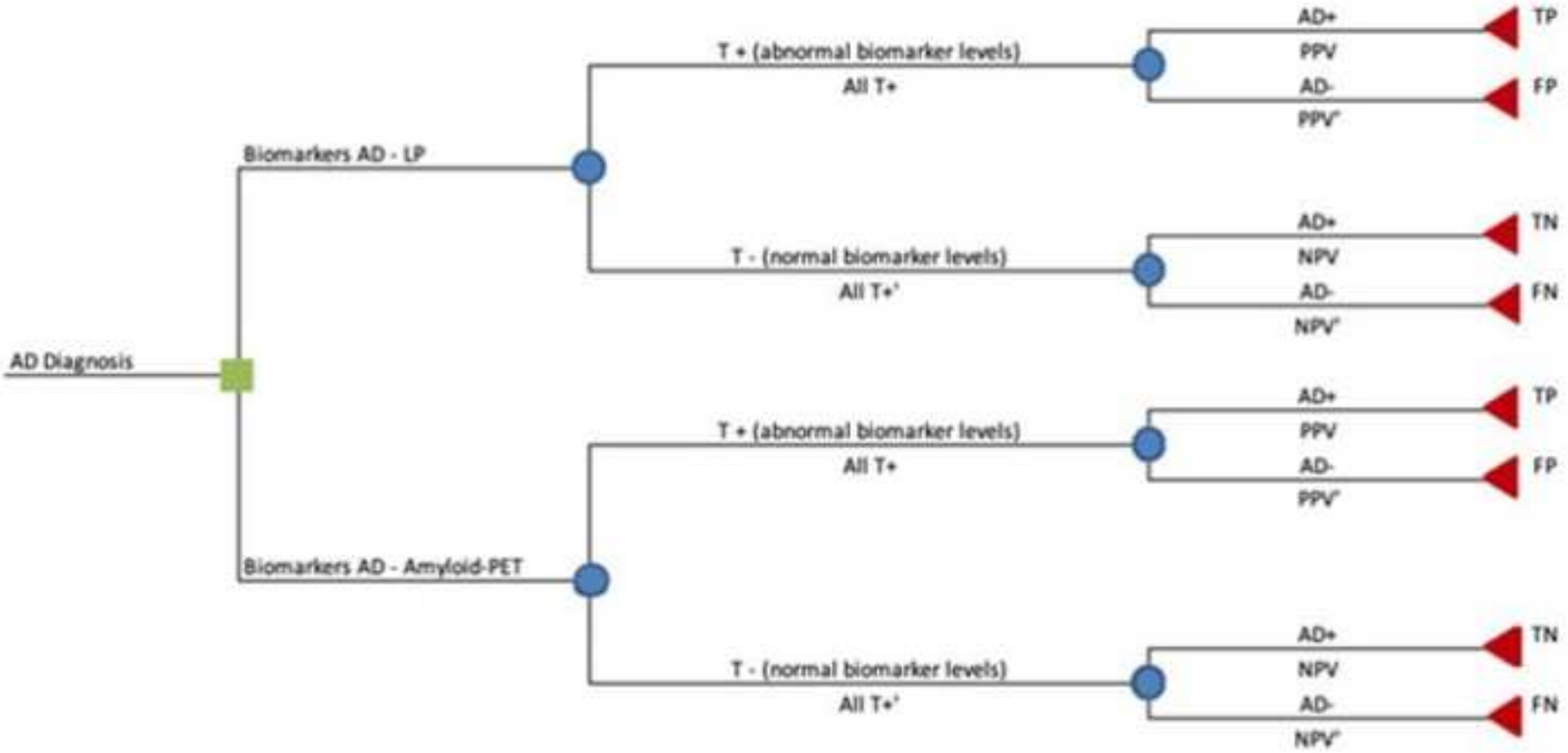

Figure 2, reviewed

Click here to access/download;Figure;Fig2.jpg

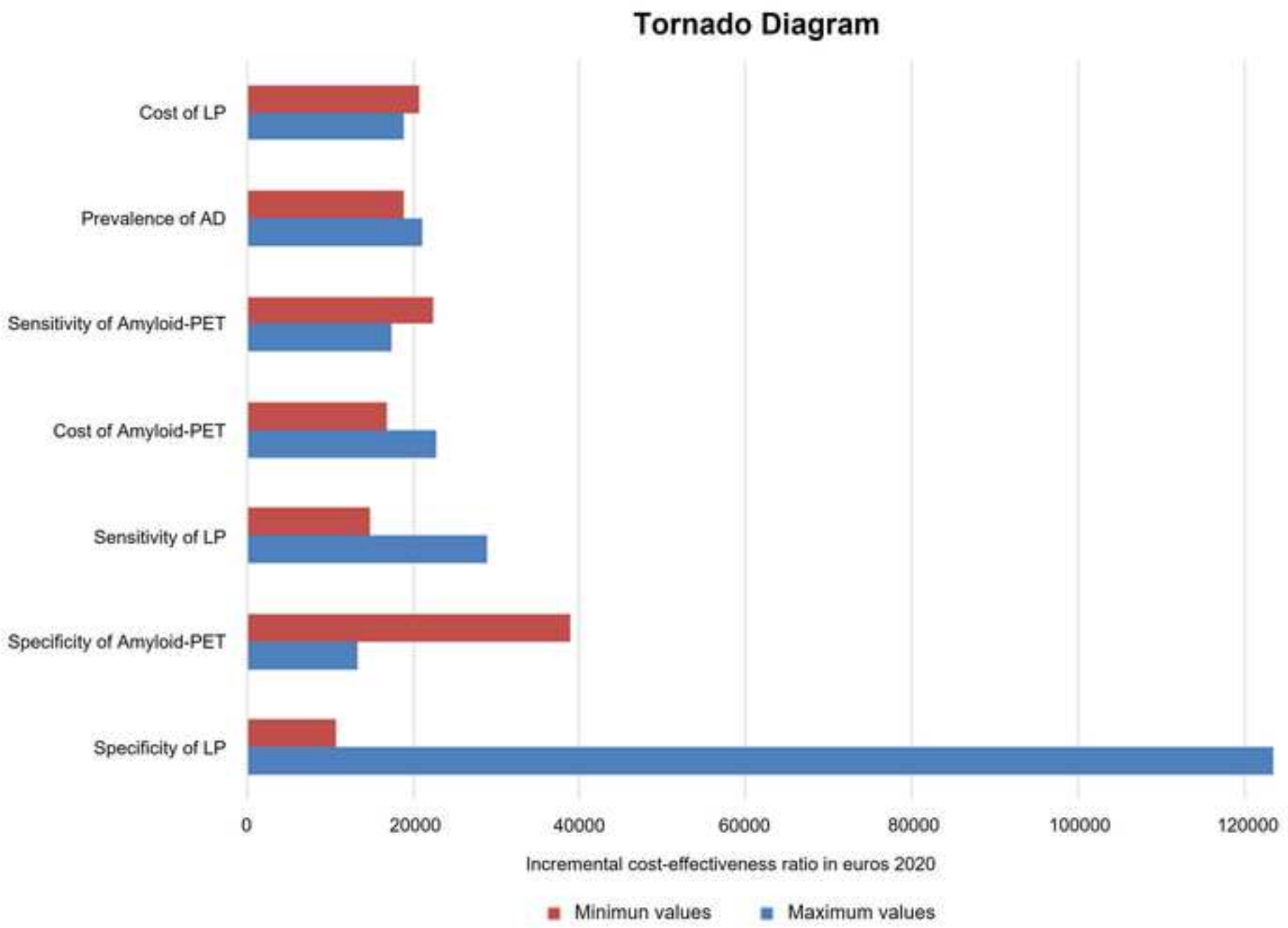

Figure 3

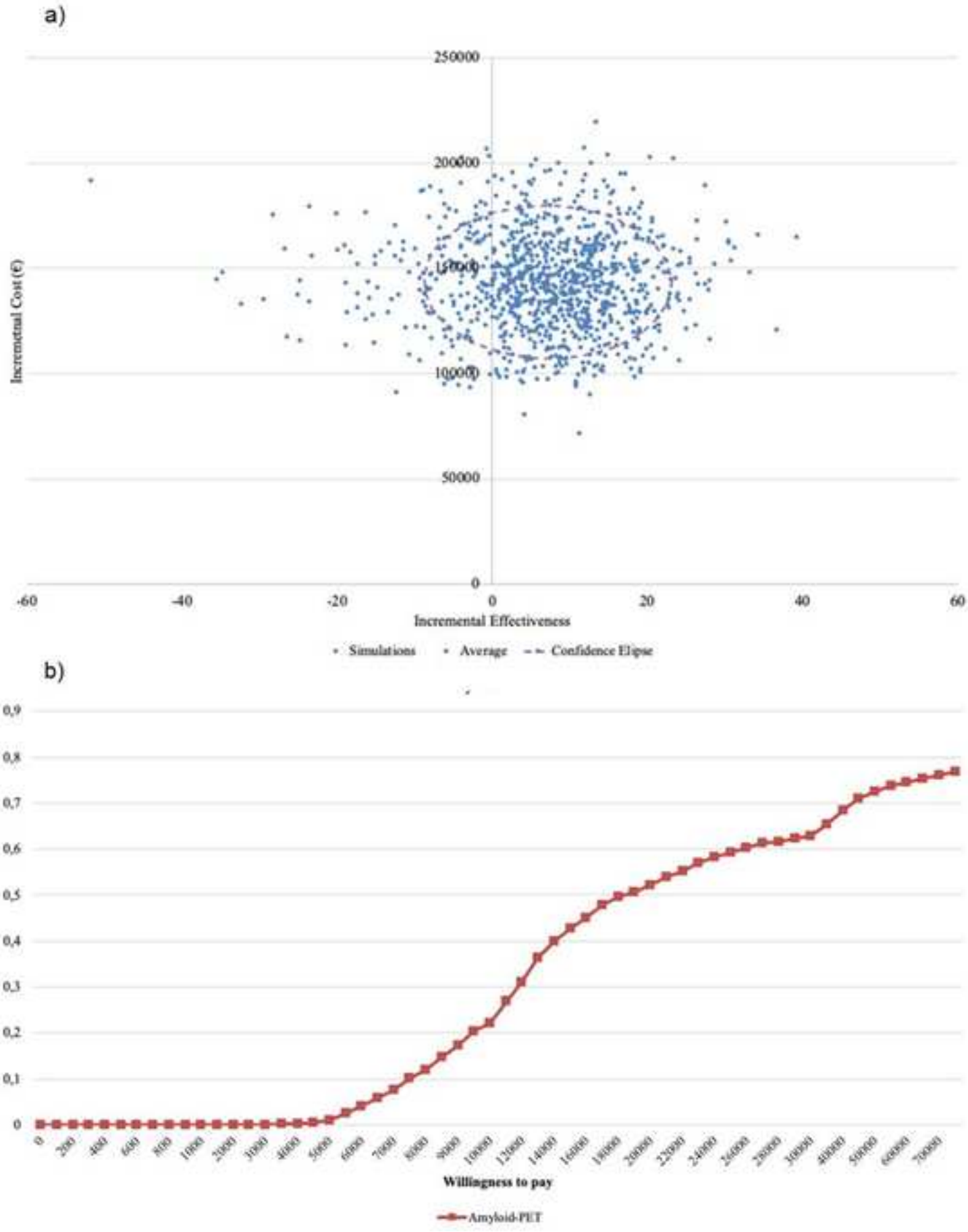

Table 1

Table 1. Model inputs (base case estimates)

Item	Estimate	Source
AD prevalence	0.2751	Authors' data proceeding from Hospital Clinic
Sensitivity of AD CSF biomarkers	0.916	Tapiola et al. 2009
Specificity of AD CSF biomarkers	0.857	Tapiola et al. 2009
Sensitivity of amyloid-PET	0.94	Chandra et al. 2019
Specificity of amyloid-PET	0.95	Chandra et al. 2019
PPV (LP)	0.714	Calculated according to Rautenberg et al. (2020) (more details in Supplementary)
NPV (LP)	0.963	Calculated according to Rautenberg et al. (2020) (more details in Supplementary)
PPV (Amyloid-PET)	0.88	Calculated according to Rautenberg et al. (2020) (more details in Supplementary)
NPV (Amyloid-PET)	0.976	Calculated according to Rautenberg et al. (2020) (more details in Supplementary)
Proportion of cohort T+ (LP)	0.3595	Calculated according to Rautenberg et al. (2020) (more details in Supplementary)
Proportion of cohort T+ (Amyloid-PET)	0.2992	Calculated according to Rautenberg et al. (2020) (more details in Supplementary)
Cost of AD CSF biomarkers (total)	€536.78	Authors' data from Hospital Clinic
Cost of day hospital for LP (including health professionals)	€255.40	Authors' data from Hospital Clinic
Cost of the LP procedure	€95.38	Authors' data from Hospital Clinic
Cost of 3 kits for biochemical analyses	€186	Authors' data from Hospital Clinic
Cost of AD CSF biomarkers (subtracting the cost of 3 kits for biochemical analyses for those who had some problem during the diagnostic procedure)	€350.78	Authors' data from Hospital Clinic
Cost of Amyloid-PET (including health professionals)	€2,170	Authors' data from Hospital Clinic
Cost of outpatient visits (one first visit + two subsequent visits) for both interventions	€218.68	Authors' data from Hospital Clinic

Key: AD: Alzheimer's disease; Amyloid-PET: amyloid-positron emission tomography; CSF: cerebrospinal fluid; LP: lumbar puncture; T+: test positive; PPV: positive predictive value; NPV: negative predictive value

Table 2. Parameters modified in the univariate sensitivity analysis

	Minimum	Maximum
Prevalence of AD	0.2164	0.3428
Sensitivity of AD CSF biomarkers	0.8244	1
Specificity of AD CSF biomarkers	0.7713	0.9427
Sensitivity of Amyloid-PET	0.91	0.979
Specificity of Amyloid-PET	0.9	1
Cost of AD CSF biomarkers	€483.10	€590.46
Cost of Amyloid-PET	€1,953	€2,387

Key: AD: Alzheimer's disease; Amyloid-PET: amyloid-positron emission tomography; CSF: cerebrospinal fluid.

Table 3 track change mode

Table 3. Results of base case cost-effectiveness analysis (€2020).

	Cost	Accurate diagnosis†	Incremental cost	Incremental accurate diagnosis ‡	ICER
Amyloid-PET	€238,868.07	94.73	€146,854.80	7.40	19,840.39
AD CSF biomarkers	€92,013.2	87.32			

†Correctly diagnosed cases per 100. ‡ Difference on correctly diagnosed cases per 100 between those who were diagnosed throughout Amyloid-PET and those who were diagnosed throughout lumbar puncture. Key: AD: Alzheimer's disease; Amyloid-PET: amyloid-positron emission tomography; CSF: cerebrospinal fluid; ICER: incremental cost-effectiveness ratio.

Table 4. Results of deterministic sensitivity analyses (€2020).

	Additional AD cases correctly diagnosed by PET compared to CSF	Costs (€)	ICER
Sensitivity of AD CSF biomarkers			
Min: 0.82	9.92	146,854.80	14,801.34
Max: 1	5.09	146,854.80	28,846.13
Specificity of AD CSF biomarkers			
Min: 0.77	13.61	146,854.80	10,786.88
Max: 0.94	1.19	146,854.80	123,467.88
Cost of AD CSF biomarkers			
Min: 483.10	7.40	153,782.37	20,776.32
Max: 509.46	7.40	139,927.23	18,904.46
Sensitivity of Amyloid-PET			
Min: 0.91	6.58	146,854.80	22,330.20
Max: 0.98	8.48	146,854.80	17,328.61
Specificity of Amyloid-PET			
Min: 0.9	3.77	146,854.80	38,878.14
Max: 1	11.03	146,854.80	13,318.58
Cost of Amyloid-PET			
Min: 1,95	7.40	124,950.42	16,881.06
Max: 2,39	7.40	168,759.18	22,799.72
Prevalence of AD			
Min: 0.22	7.81	146,854.80	18,811.04
Max: 0.34	6.94	146,854.80	21,176.87

Key: AD: Alzheimer's disease; Amyloid-PET: amyloid-positron emission tomography; CSF: cerebrospinal fluid; ICER: incremental cost-effectiveness ratio; Max: maximum; Min: minimum.

Table 5. Results of probabilistic sensitivity analysis (€2020)

	Cost	Accurate diagnosis†	Incremental cost	Incremental accurate diagnosis‡	ICER
Amyloid-PET	€238,931.83 ±1,452.05	94.54 ±0.47	€143,556.32 ±1,401.04	7.13 ±0.62	22,340.93 ±26,353.39
AD CSF biomarkers	€95,375.51 ±440.59	87.41 ±0.40			

† Correctly diagnosed cases per 100. ‡ Difference on correctly diagnosed cases per 100 between those who were diagnosed throughout Amyloid-PET and those who were diagnosed throughout LP. Key: ±: ± 95% confidence interval; Amyloid-PET: amyloid-positron emission tomography; AD: Alzheimer's disease; CSF: cerebrospinal fluid; ICER: incremental cost-effectiveness ratio.