

# Cost-Utility of Using Alzheimer's Disease Biomarkers in Cerebrospinal Fluid to Predict Progression from Mild Cognitive Impairment to Dementia

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# Cost-Utility of Using Alzheimer's Disease Biomarkers in Cerebrospinal Fluid to Predict Progression from Mild Cognitive Impairment to Dementia

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## Abstract.

**Background:** Diagnostic research criteria for Alzheimer's disease support the use of biomarkers in the cerebrospinal fluid (CSF) to improve the accuracy of the prognosis regarding progression to dementia for people with mild cognitive impairment (MCI).

**Objective:** The aim of this study was to estimate the potential incremental cost-effectiveness ratio of adding CSF biomarker testing to the standard diagnostic workup to determine the prognosis for patients with MCI.

**Methods:** In an early technology assessment, a mathematical simulation model was built, using available evidence on added prognostic value as well as expert opinion to estimate the incremental costs and quality-adjusted life years (QALYs) of 20,000 virtual MCI patients with (intervention strategy) and without (control strategy) relying on CSF, from a health-care sector perspective and with a 5-year time horizon.

**Results:** Adding the CSF test improved the accuracy of prognosis by 11%. This resulted in an average QALY gain of 0.046 and €432 additional costs per patient, representing an incremental cost-effectiveness ratio of €9,416.

**Conclusion:** The results show the potential of CSF biomarkers in current practice from a health-economics perspective. This result was, however, marked by a high degree of uncertainty, and empirical research is required into the impact of a prognosis on worrying, false-positive/negative prognosis, and stigmatization.

Keywords: Alzheimer's disease, cerebrospinal fluid, cost-utility, economic evaluation, mild cognitive impairment, prognosis, risk

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## INTRODUCTION

With a global prevalence of 47 million [1] and a corresponding economic impact of US\$ 818 billion [2], dementia imposes a substantial burden on societies worldwide. Limited national care budgets force governments and health insurers to reimburse only a selection of all available healthcare technologies. These choices are ideally based on cost-effectiveness evidence, such that the available budget is spent on the selection of interventions that result in the maximum societal health gain.

Clinical guidelines for suspected Alzheimer's disease (AD) recommend a standard assessment of clinical history, cognition, behavioral symptoms, co-morbidities, and neuroimaging in patients with suspected dementia [3]. In the last decade, proposals for new research-based diagnostic criteria for AD have been developed, including advanced diagnostic technologies that enable the early identification of brain abnormalities [4–7]. As regards CSF biomarkers, the evidence base for these recommendations is formed by studies of diagnostic and prognostic accuracy [8].

Diagnostic tests are, however, no exception to any other health intervention [9, 10]; because they consume part of the health care budget means that this part cannot be spent on an alternative intervention and its corresponding opportunity to gain health. To support reimbursement by governments or health insurers, diagnostic tests should therefore be evaluated in terms of incremental cost-effectiveness using clinical or quality-adjusted life year (QALY) outcomes. This allows intervention effects to be compared between different diseases, as reflected by different outcomes, to enable a well-informed decision to be made about reimbursement.

A few studies have attempted to reflect the clinical utility of CSF biomarkers by assessing the impact on diagnostic decision making [11, 12] or diagnostic confidence [13] of adding CSF biomarkers to standard clinical tests. The results were mixed, and the studies did not report on health effects. A systematic review on the effect of early identification of AD hallmarks did not find any empirical evidence of health benefits derived from persons with and without identified AD-related brain abnormalities in pre-dementia [14]. Nevertheless, this and other reviews reported on the potential benefits and harms of early [14] and genetic testing [15] or a timely diagnosis [15] of AD or other neurodegenerative disorders [16]. This includes benefits related to decreased anxiety if the

cause is found not to be AD, management of cognitive symptoms to reduce the related burden, and planning for future care and personal adjustments to prevent burden or crisis situations when symptoms increase. Potential harms include the impact of stigmatization, anxiety and depression after a diagnosis is communicated (whether true or false), and the side-effects of the lumbar puncture, such as headache. In the absence of a registered treatment, no benefits can be expected in terms of slowing down the disease progression in the pre-dementia stage of AD.

Previous studies on the cost-effectiveness of using CSF markers have either disregarded any potential health impact [17] or assumed a hypothetical disease-modifying treatment [18–22] to be decided upon based on CSF test results. Such results only reflect a limited part of the potential impact of CSF testing.

The lack of empirical evidence on health effects related to CSF testing limits the appraisal of this technology to support reimbursement decisions. Further advancement of the health-economic assessment of CSF requires identifying the topics for future empirical research. This could be done in an early technology assessment [23], which could identify drivers of uncertainty as well as assess the sensitivity of health-economic outcomes to different sets of assumptions on parameters for which evidence is lacking. Such early assessment could also determine the potential of CSF tests, which, if it proves to be substantial, would argue for supporting further empirical research into input parameters for which little evidence is available. Finally, it could aid in the development of a simulation framework that reflects clinical practice and aggregates the pieces of evidence from various sources. The aim of this study was to estimate the potential incremental cost-effectiveness ratio of adding CSF biomarker testing to the standard diagnostic workup to determine the prognosis for patients with MCI. An early technology assessment was performed by means of a simulation study using existing evidence as well as plausible assumptions on potential health benefits and harms, without evaluating any hypothetical treatment.

## MATERIALS AND METHODS

The potential cost-effectiveness of CSF was estimated using a decision model that simulates the diagnostic test workup in usual care to establish a prognosis for progression to dementia (by means of predictive values using a logistic regression model)

and comparing this with a simulation of a situation in which CSF biomarkers are added to the usual-care diagnostic test workup to establish a prognosis for progression to dementia (using the same logistic regression model but with CSF biomarkers added). This was done for a group of virtual patients who visit a memory clinic for the first time and have been diagnosed with MCI. The model estimates the incremental costs and effects for a strategy in which the prognosis is based on the diagnostic workup recommended for usual care and a strategy in which the prognosis is based on adding a CSF test to the diagnostic workup recommended for usual care. No treatment effects were reflected in the model because currently none are recommended for MCI. The Supplementary Material describes in detail the model structure, data analysis, consistency, and results. The model code is available on <http://www.smard.org> or upon request to the corresponding author.

In the domain of public health, a progression to any-type dementia can be considered more important than identifying the cause of this progression as being AD, vascular disease, or other. Hence, we focused on the prognosis for progression to any-type dementia rather than the diagnosis of its sub-types. Nevertheless, since the underlying cause is required to determine the prognosis, this study partly represents the value of using CSF biomarkers for diagnosing the underlying pathology.

### *Model structure*

The simulation started by creating a virtual group of individual MCI patients and their characteristics of age, gender, level of education, underlying neurodegenerative disease (present or absent), CSF biomarker values (amyloid- $\beta$ 1-42, total tau, and phosphorylated tau), cognition, memory, and medial temporal atrophy on MRI. For each patient, the following events were simulated: 1) a prognosis consisting of a probability of developing any-type dementia; 2) one or more follow-up visits to a memory clinic for a clinical evaluation; 3) progression to dementia; and 4) death. Simulated effects also included the impact of the prognosis in terms of reduced worrying and stigmatization, the impact of a false-positive/negative prognosis, and the impact of lumbar puncture side-effects on health-related quality of life (HrQOL). Simulated costs included the visits to the clinic, lumbar puncture, and costs related to MCI and dementia. See Fig. 1 for a simple overview of the model structure.

The model was based on various assumptions, such as: 1) a patient with no neurodegenerative disease will never develop dementia; 2) a patient with a neurodegenerative disease will develop dementia within the model's time frame of 5 years; 3) dementia is irreversible; and 4) the probability of dementia progression corresponds to the dementia prognosis and degree of certainty communicated to a patient. A full list of assumptions can be found in the Supplementary Material §2.4.

### *Control and intervention strategy*

The model simulated a control strategy, which reflected the effects of a prognosis of progression to dementia over a 5-year period using the standard test workup [3], and an intervention strategy, in which CSF biomarker results are added to this workup. The prognosis was established using a prediction model [24] based on demographic information and results from tests on cognition, depression, and neuroimaging, and a prediction model adding CSF test outcomes to the first prediction model.

### *Preparatory data analyses*

Both the characteristics of the virtual patients at their initial visit and their risk of progression to dementia were simulated using the results of a study by Handels et al. [24] based on set of merged data from different cohort studies.

The decision model simulated 20,000 virtual patients and their characteristics using random draws from the study participants' distribution and correlation structure. Table 1 represents the characteristics of the merged dataset and of the characteristics of the simulated virtual patients based on the averages and distributions of the patients in the merged dataset.

Each virtual patient's prognosis was simulated by applying a dementia progression prediction model [24] to the characteristics of the 20,000 simulated patients. A prognosis was a predicted probability of progression to dementia. Two prognoses were simulated: one representing the control strategy (using all test information except CSF biomarkers) and one representing the intervention strategy (using all test information including CSF biomarkers).

Regular follow-up visits were simulated if the prognosis (i.e., predicted probability of progression to dementia) was positive (i.e., a predicted probability  $\geq 0.50$ ) or uncertain. Clinical experts considered a prognosis uncertain if the probability was higher

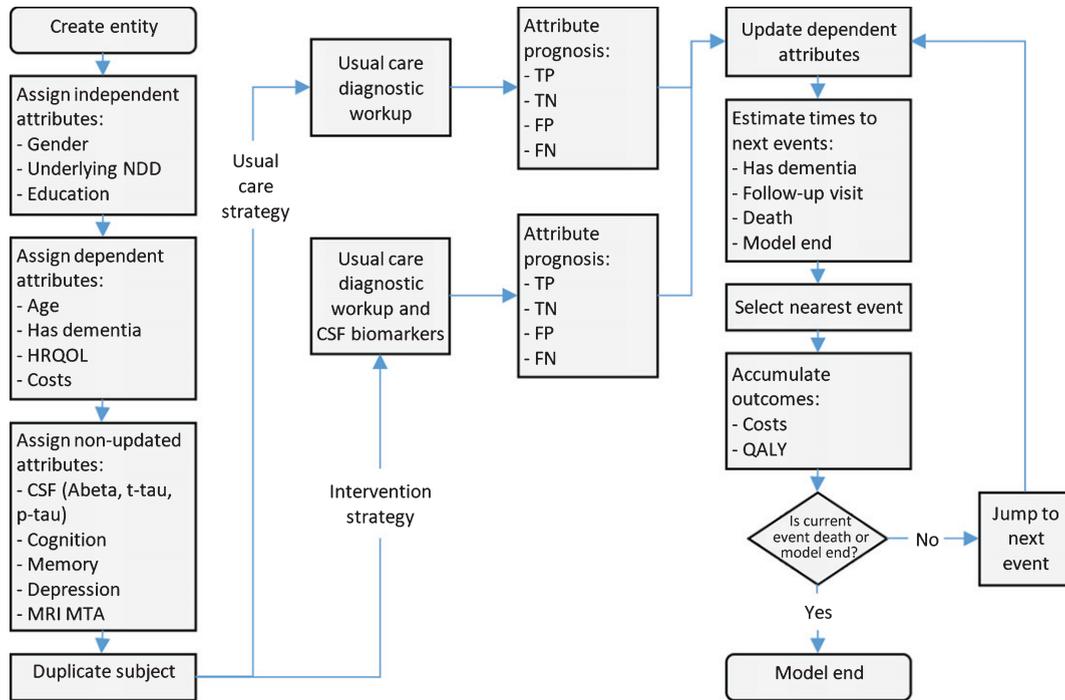


Fig. 1. Basic model structure (abbreviations: CSF, cerebrospinal fluid; FN, false-negative prognosis; FP, false-positive prognosis; HrQOL, health-related quality of life; MRI MTA, medial temporal lobe atrophy on magnetic resonance imaging; NDD, neurodegenerative disorder; TN, true-negative prognosis; TP, true-positive prognosis; QALY, quality-adjusted life year).

Table 1  
The observed baseline characteristics of 250 participants in the cohort studies analyzed by Handels et al. [24] and the simulated baseline characteristics of the 20,000 patients entering the decision model

Characteristic	Original study		Simulated cohort	
	Mean (SD) or n (%)	Range	Mean (SD) or n (%)	Range
Age	68.6 (7.5)	52.0 to 89.0	68.7 (8.1)	35.2 to 101.8
Female gender	111 (44%)	NA	45%	NA
Education, y	11.2 (3.1)	4 to 18	11.2 (3.2)	-2 to 24
MMSE	26.9 (2.4)	18 to 30	27.0 (2.4)	12 to 30
WLT delayed recall z-score	-1.6 (1.2)	-5.6 to 2.3	-1.6 (1.2)	-6.2 to 3.7
Depression <sup>1</sup>	0.3 (0.6)	0 to 2	0.3 (0.5)	0 to 4
MRI MTA left and right	2.3 (1.8)	0 to 6	2.2 (1.7)	0 to 6
CSF Aβ	666 (296)	157 to 1538	661 (268)	37 to 1666
CSF t-tau	446 (237)	52 to 1179	457 (262)	0 to 1396
CSF p-tau	71 (30)	16 to 172	69 (14)	25 to 133
Progression to dementia (events)	99 (40%)	NA	25%	NA

Table partly copied from Handels et al. [24] with permission of the author. <sup>1</sup>0=no symptoms, 1=mild symptoms, 2=moderate symptoms. CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; MTA, medial temporal lobe atrophy; WLT, word learning test; SD, standard deviation.

than 0.24, and on average recommended to follow up patients every 9.3 months for a maximum of 5 years. Patients with a low probability of decline (<0.24) were sent home. If the test result was false-negative, they returned to the clinic 1 year after progression to dementia occurred.

The following aspects were assumed to influence the HrQOL of each simulated patient: MCI syndrome, worrying about progression to dementia,

false-positive prognosis, false-negative prognosis, stigmatization, and lumbar puncture adverse effects. These effects were expressed in terms of a utility, a number ranging from 0 (reflecting the worst possible health state or death) to 1 (reflecting a perfect health state). Each simulated patient was assumed to worry about their possible progression to dementia before having visited a medical professional. The clinical experts in our study estimated that worrying

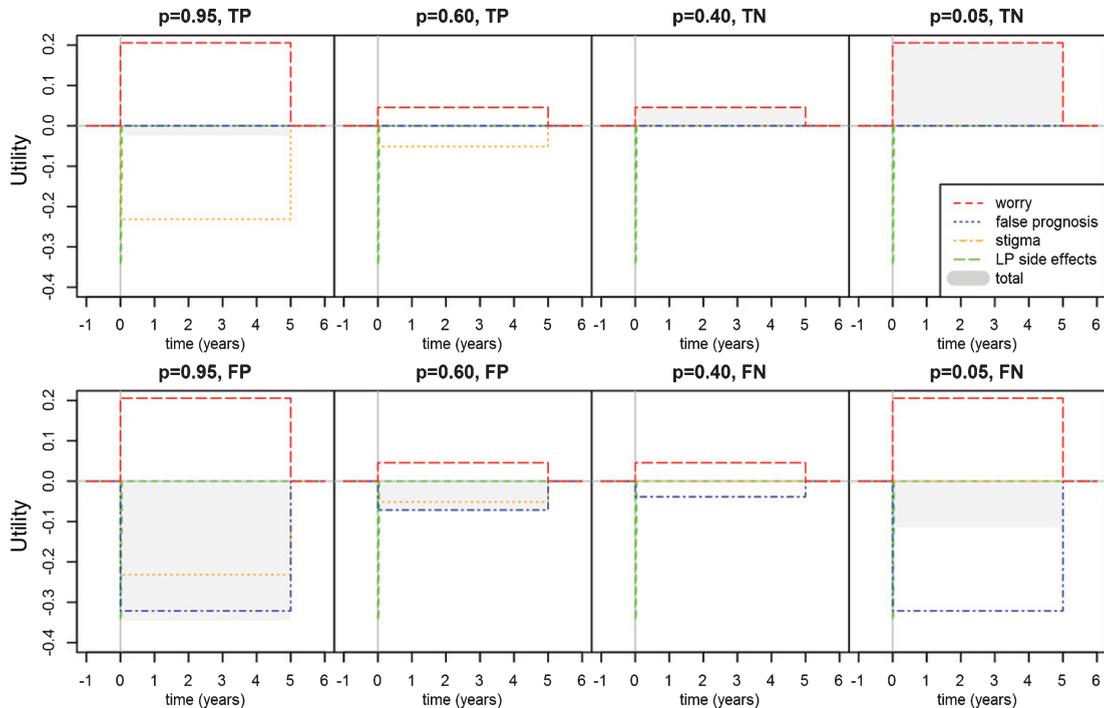


Fig. 2. Overview of the assumed impact of reduced worrying, false-positive/negative prognosis, stigma and lumbar puncture side-effects on a patient's utility. FN, false-negative prognosis; FP, false-positive prognosis; TN, true-negative prognosis; TP, true-positive prognosis; LP, lumbar puncture.

represents a utility decrease of 0.23. This effect was assumed to reflect maximum uncertainty at a prognostic dementia probability of 0.50. After testing, a specific prognosis was established for the patient. This prognosis was assumed to correspond linearly to a decreased disutility relating to worrying about dementia. For example, a prognosis of 0.95 reflects a high certainty of progression to dementia, resulting in a reduction of worrying about progression to dementia and thus an increase in utility (see left top Fig. 2, red dashed).

However, this positive prognosis also corresponds to a stigmatizing effect of being labelled as high probability of progression to dementia, resulting in a decrease of utility. The clinical experts estimated this as a 0.26 utility decrease, and it was assumed to correspond linearly to the prognostic dementia probability (0.26 at a probability of 1 or when diagnosed with dementia, and 0 at a probability of 0.50; see Fig. 2, yellow dashed). The clinical experts estimated the utility decrease due to a false-positive prognosis (probability of progression to dementia between 0.50 and 1 whereas progression to dementia does actually not takes place within 5 years) and a false-negative prognosis (probability of progression

to dementia between 0 and 0.50 whereas progression to dementia actually takes place within 5 years) at 0.36 and 0.19, respectively. These effects were also assumed to correspond linearly to the probability (see Fig. 2, blue dashed). The clinical experts estimated various impacts of side-effects of a lumbar puncture. These were combined with evidence on the probability of occurrence and duration [25] (see Table 2). Details on the method of obtaining expert opinion are included in the Supplementary Material (§3.2.12). Utility scores were linearly interpolated between events to estimate QALYs.

Costs related to MCI and dementia as well as for a clinical visit and the lumbar puncture were obtained from various Swedish sources [26, 27] (see Table 2), reflecting a health-care sector perspective. Prices were converted to Euro 2015 estimates.

### Outcomes

The primary outcome was the average incremental net monetary benefit of the intervention strategy over a period of 5 years. This net monetary benefit was calculated by valuing 1 QALY at €20,000 [28] and subtracting the costs from it. A positive incremental

Table 2  
Model input parameters (2015 price estimates)

Category	Parameter	Parameter estimate for individual
<i>Patient characteristics</i>	age, gender, education, MMSE, word learning test, depression, MRI MTA, A $\beta$ , t-tau, p-tau	See Supplementary Material §3.2.1
<i>LP related</i>	Prognostic probability	logistic regression prediction model
	Headache	Bootstrap sampling: none: $p=0.91$ ; mild: $p=0.06$ ; moderate: $p=0.03$
	Headache duration (in days)	Bootstrap sampling: 0.5 ( $p=0.26$ ); 1.5 ( $p=0.24$ ); 3 ( $p=0.28$ ); 7 ( $p=0.22$ )
<i>Decisions</i>	Serious complication	$p=0.01$
	Serious complication duration (years)	1.1/52
	Cut-off probability uncertain prognoses	0.24
<i>Time to event (years)</i>	Follow-up duration (years)	5
	Regular follow-up visit	9.3/12
	Patient with underdiagnosed NDD revisits the clinic	1.0
	Re-establish prognosis	5
	Progression to dementia	Beta distribution: $\alpha=1.09$ ; $\beta=2.19$
<i>HrQOL utilities</i>	Death	Sampling from survival table
	MCI	0.72
	Dementia	0.63
	Worrying	-0.23
	Stigma of NDD	-0.26
	Impact of FP	-0.36
	Impact of FN	-0.19
	LP mild headache	-0.10
	LP moderate headache	-0.16
	LP serious complication	-0.22
<i>Costs (€, 2015)</i>	Base visit	1210
	Regular follow-up visit	787
	Lumbar puncture	621
	Annual care MCI	3524
	Annual care mild dementia	10219

CBS, Statistics Netherlands; EP, expert opinion; FN, false-negative prognosis; FP, false-positive prognosis; HrQOL, health-related quality of life; k, shape parameter; LP, lumbar puncture; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; MTA, medial temporal atrophy; NDD, neurodegenerative disorder; NM, not modelled; p, probability; pc, percentile; p-tau, phosphorylated tau; SE, standard error; t-tau, total tau;  $\alpha$ , shape parameter;  $\beta$ , shape parameter;  $\theta$ , scale parameter.

net monetary benefit reflects the preferred situation of a health gain in terms of QALY improvement at reasonable costs or cost savings (or cost savings at a reasonable QALY loss). Secondary outcomes were total incremental costs, incremental QALYs (1 QALY reflects one year in full HrQOL), concordance index (reflecting the accuracy of the prognosis) and the proportion correctly reclassified.

### Sensitivity analysis

The clinical expert opinions, the empirical evidence and the various assumptions made in this simulation study were subject to a degree of uncertainty, which resulted in uncertainty in the estimated costs and QALYs. In a probabilistic sensitivity analysis, parameter uncertainty was assessed by running the model 10,000 times, each time using a different

set of plausible input values by randomly drawing them from their parameter distributions (see Table 2) (see Supplementary Material §3.4 for details).

## RESULTS

### Main outcomes

The simulated sample of 20,000 virtual patients had an average age of 69 years, 45% were female, and they had an average MMSE of 27.0 and a 5-year prevalence of progression to dementia of 25% (see Table 1). In 46% the risk of progression to dementia between before and after using CSF tests was 0.10 or more (on a scale from 0 to 1). In this subsample, 68% of the risk changes was correct (meaning an increased risk over time and actually progressing

to dementia, or a decreased risk over time and not actually progressing to dementia). The concordance index was 0.705 for the control strategy and 0.801 for the intervention strategy.

The intervention strategy resulted in more positive prognoses (14% versus 10% in the control strategy), more false-negative prognoses (5% versus 4% in the control strategy), fewer false-positive prognoses (16% versus 20% in the control strategy), and more follow-up visits (on average 2.04 visits per patient versus 1.80 visits in the control strategy) with corresponding impact on QALYs and costs.

The simulation estimated a 0.046 mean QALY gain and €432 mean additional costs per patient when adding the lumbar puncture to the usual-care diagnostic workup for the prognosis of progression to dementia in MCI. This resulted in an incremental cost-effectiveness ratio of €9,416. Assuming a willingness-to-pay of €20,000 per QALY, the incremental net monetary benefit was €486.

*Uncertainty*

These outcomes were subject to uncertainty. The incremental cost-effectiveness plane in Fig. 3 reflects how the uncertainty of most input parameters in the model (e.g., expert opinions and risk prediction coefficients) resulted in uncertainty in the costs and QALY outcomes. Of the plausible scenarios, 95% had incremental costs of between €-767 and €1,165, incremental QALYs of between -0.145 and 0.314 and incremental net monetary benefit of between €-3,829 and €6,440.

Scenarios with a negative net monetary benefit are unwanted. These are reflected by the red-shaded area in Fig. 3; the blue dots in the left top quadrant (33% of all plausible scenarios), indicating an HrQOL loss at higher costs; and the blue dots in the right top quadrant above the willingness-to-pay threshold of €20,000 per QALY (12%), indicating the unwanted situation of improved QALY but at unacceptably high costs. Sixteen percent of all plausible scenarios resulted in the preferred outcome of improved QALY and cost savings, and 40% led to improved QALY outcomes at acceptable costs below the willingness-to-pay threshold (reflected by the green-shaded area in Fig. 3). Less than 1% fell in the lower left quadrant, indicating a QALY loss at lower costs. Assuming a willingness-to-pay of €20,000 for a gain of 1 QALY, 56% of all plausible scenarios were cost-effective. In other words, there was a 56% chance that adding the lumbar puncture to

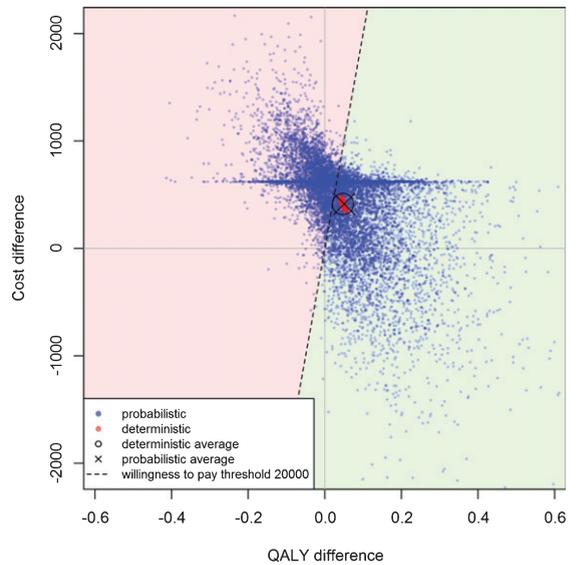


Fig. 3. Incremental cost-effectiveness plane. Each blue dots represents the average incremental costs and average incremental QALYs for 5,000 simulated patients in the control strategy and intervention strategy, using 10,000 different sets of random parameter draws from a plausible distribution, reflecting parameter uncertainty. The red dots represent 5,000 simulated patients in the deterministic mode reflecting stochastic uncertainty. The black open circle and cross represent the average incremental costs and effects of the deterministic and probabilistic results, respectively. The green shaded area to the right of the dashed line represents scenarios cost-effective at a willingness-to-pay of €20,000 per incremental QALY; the red shaded area to the left of the dashed line represents scenarios that are not cost-effective.

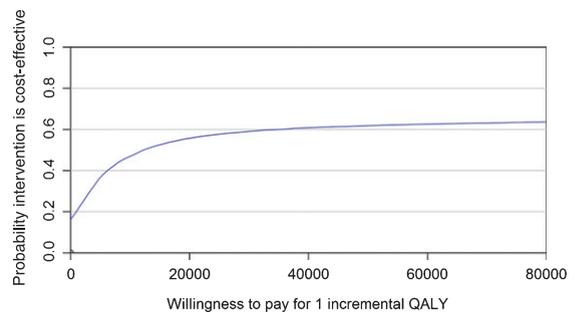


Fig. 4. Incremental cost-effectiveness acceptability curve representing the probability of CSF being cost-effective at various levels of willingness to pay for 1 QALY.

the usual-care diagnostic workup would result in cost-effective care. Assuming a willingness-to-pay of €80,000 per QALY, this was 64% (see Fig. 4). In other words, 64% of the plausible scenarios were cost-effective (implicates 36% were not).

The univariate sensitivity analysis showed the impact of various specific plausible scenarios on the cost-effectiveness of adding CSF testing. The costs of

the lumbar puncture, the impact of stigma, the impact of reduced worrying, the impact of a false-negative prognosis, and the cut-off value at which the probability that a person will be followed up had the highest impact on the cost-effectiveness outcomes (see Supplementary Material §5.2). For example, a higher assumed impact of a false-negative prognosis by the clinical experts resulted in a lower incremental net monetary benefit, because the intervention strategy resulted in more false-negative prognoses (5% versus 4% in the control strategy). Since the intervention strategy resulted in fewer false-positive prognoses (16% versus 20% in the control strategy), its relation with incremental monetary benefit was opposite for the impact of a false-positive compared to the impact of a false-negative. Similarly, since more positive prognoses occurred in the intervention group (14% versus 10% in the control strategy), a higher stigmatizing effect resulted in a lower incremental net monetary benefit. The uncertainty about the complications of a lumbar puncture and the impact and duration of headache had almost no impact on the cost-effectiveness.

Omitting the specific uncertainty from the beta estimates of the logistic regression prediction model resulted in 74% and 91% of all plausible scenarios being cost-effective at a willingness-to-pay of €20,000 and €80,000 per QALY, respectively (see Supplementary Material §5.2).

## DISCUSSION

Determining CSF biomarkers in addition to the usual-care diagnostic workup to establish the prognosis for progression to dementia resulted in an average potential gain of 0.046 QALYs at €432 additional costs. This corresponds to a potential cost-effectiveness ratio of €9,416 per QALY. These estimates were, however, highly uncertain, because even assuming a willingness-to-pay of €80,000 per QALY gained, the likelihood that adding CSF biomarkers is cost-effective was only 64%, corresponding to a 36% likelihood that it is not.

This early technology assessment reflected the potential value of CSF testing in the pre-dementia state, in which no treatment is available, by estimating plausible impacts of reduced worrying, stigma and false-positive and false-negative prognosis. The health-economic outcomes show that on average the benefits could outweigh the harms, thus indicating

the potential of CSF testing for prognostic purposes. However, the uncertainty in the results was considerable and makes it difficult to draw strong conclusions for the purpose of reimbursement by governments or health insurers. Nevertheless, our study yielded various useful insights.

The model showed the combined impact of adding CSF biomarkers to the usual-care diagnostic workup. The cost-effectiveness estimate can be seen as a set of trade-offs. For example, the investment in performing a lumbar puncture reduced the costs of following up patients. Another example is that a gain in QALYs due to reduced worrying because of a correct positive prognosis as a result of the lumbar puncture came at the cost of a loss of QALYs due to the stigmatizing effect of the positive prognosis. These set of trade-offs indicate the importance of a holistic viewpoint and moving forward from the typical assumption that improved prognostic or diagnostic accuracy in terms of sensitivity and specificity reflects clinical utility. Despite the positive cost-effectiveness outcome of this study, the QALY gain of 0.046 was small, representing an average quality-of-life improvement of 0.009 (on a scale of 0 representing death and 1 representing full quality of life) for a duration of 5 years, as mortality did not differ between the control and intervention strategies.

### *Comparison with other studies*

There have been other studies evaluating the incremental cost-effectiveness of using CSF biomarkers. The majority of these studies [18–22] used a hypothetical future scenario in which disease-modifying treatment is available that significantly reduces the rate of progression. Such studies have evaluated the impact of using a CSF test on decision making for treatment, and showed that this was potentially cost-effective. A study by Valcárcel-Nazco et al. [17] evaluated CSF biomarkers for decisions about off-label Donepezil treatment in MCI. They showed lower costs per correctly diagnosed patient when using CSF biomarkers (€1,336) versus using standard clinical diagnostic criteria (€3,167), on the assumption that this off-label treatment is both effective and reduces costs in MCI. Potential non-medical impacts such as reduced worrying, false-positive/negative prognosis and stigmatization were not assessed, as the study disregarded HrQOL. Our study is the first to attempt to assess the value of CSF testing in actual current clinical practice in terms of HrQOL and costs.

### Recommendations

We recommend empirical research into the parameters to which the health-economic outcomes were most sensitive. These included the impact of stigma, the impact of reduced worrying and the impact of a false-negative prognosis. Uncertainty caused by the uncertain costs of performing a lumbar puncture and the uncertain costs of performing a follow-up visit could be solved by applying the fixed price from the specific hospital in which the CSF technology is to be implemented. The uncertainty in the cut-off value to decide about following up patients should be the topic of an optimization analysis, as this can generate the optimal cut-off value to ensure cost-effective application of CSF testing in practice. Furthermore, our results indicated that the evidence base on side effects due to CSF assessment is sufficiently large. Uncertainty due to the logistic regression prediction model was probably overestimated, as data from other studies have been collected in other studies but were not requested by us.

The model framework supported the concept of including potential health effects for the evaluation of a diagnostic test. Although the discrete event simulation increased the level of complexity compared to the well-established Markov model, it allowed the inclusion of various levels of uncertainty without losing detail due to categorizing them into states [24]. If health effects do indeed occur within the relatively short time period of 5 years, a trial-based economic evaluation could serve as an alternative, though involving a risk of bias if there is no option of blinding for undergoing a lumbar puncture and for interpreting the test result. Nevertheless, a model framework has the potential to identify subgroups for whom cost-effectiveness is high [29].

### Limitations

The simulation model is a simplistic representation of the real-world situation. Actual current practice is more complex and heterogeneous, especially in terms of the medical decisions made with or without relying on biomarkers and between positive, negative or intermediate test outcomes, which were not taken into account in our study. Furthermore, the way a probability or risk is communicated to and received by a person most likely varies considerably. Discounting was disregarded, as insufficient resources were available to build this into the model. Discounting would likely lower the cost-effectiveness, as costs occurred

at the start, while savings due to reduced follow-ups and effects occurred later in time, although the impact is likely to be low, due to the relatively short time period. By adopting a health-care sector perspective, we omitted out-of-pocket expenses such as travel costs, informal caregiving time, and productivity losses, factors for which it is difficult to indicate whether they would have led to over- or underestimation of the cost-effectiveness. The results of this study are therefore mainly useful to estimate the potential of CSF testing for scientific purposes, rather than to advise upon clinical management in practice or policy. These limitations were of secondary relevance to the exploratory nature of this study, to show the balance regarding the non-medical impact of testing. Nevertheless, our extensive sensitivity analysis covered a wide range of plausible inputs and methodological choices made, making their impact on results transparent (see Supplementary Material §6 for details).

Expressing health effects of diagnostic information in terms of QALYs might be challenging. Scales like the ICECAP provide an index of capabilities [30], which could be more sensitive to the effects of diagnostic information, and constitute an alternative to EQ5D-based utility scores.

### Conclusions

Adding CSF tests to the usual-care diagnostic workup for the prognosis of progression to dementia in persons with MCI was cost-effective when relying on expert opinion about its expected impact in current practice. This result was, however, highly uncertain and calls for empirical research into the impact of a prognosis on the aspect of reducing worrying, false-positive and false-negative prognosis, and stigmatization.

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## SUPPLEMENTARY MATERIAL

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