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Early cost-utility analysis of general and cerebrospinal fluid-specific Alzheimer's disease biomarkers for hypothetical disease-modifying treatment decision in mild cognitive impairment

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Abstract

Introduction: The study aimed to determine the room for improvement of a perfect cerebrospinal fluid (CSF) biomarker and the societal incremental net monetary benefit of CSF in subjects with mild cognitive impairment (MCI) assuming a hypothetical disease-modifying Alzheimer's disease (AD) treatment.

Methods: A decision model compared current practice to a perfect biomarker and to two strategies positioning CSF as add-on test when current practice concluded the presence or absence of AD.

Results: The simulated MCI population was aged on average 68.3 and 49% had AD. The room for improvement by the perfect CSF test was 0.39 quality adjusted life years, €33,622 ($43,372) savings, 2.0 potential beneficial treatment years, and 1.3-year delay in dementia conversion.

Discussion: The results indicated more potential benefit from a biomarker positioned to verify subjects who are not expected to have AD (i.e., to prevent undertreatment) rather than to verify subjects expected to have AD (prevent overtreatment). Sensitivity analyses explored different CSF positions.

Keywords: Alzheimer's disease; Mild cognitive impairment; Cerebrospinal fluid; Biomarker; Decision analytic modeling; Economic evaluation; Cost-utility; Hypothetical disease-modifying treatment

1. Introduction

With a global prevalence of 35.6 million and a corresponding economic impact of US $604 billion dementia has a substantial burden on societies worldwide [1,2]. There has been a growing interest in biomarkers in cerebrospinal fluid (CSF), positron emission tomography, and magnetic resonance imaging [3] to identify Alzheimer's disease (AD) pathology in patients with the predementia stage mild cognitive impairment (MCI) for the development of drugs that prevent conversion to dementia. Despite its research status, CSF is finding its way in clinical practice [4] although the decision to adopt it should depend on the improvement of a patient's health and, in a resource-constrained health care system, on cost-utility.

Economic evaluations have evaluated the added value of pathways from test to treatment (test-treat) of AD biomarkers [5], although none focussed on the MCI phase since treatment is absent [6].

By identifying the room for improvement, that is, the benefits when the current practice diagnostic accuracy is

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maximally improved by a perfect biomarker test, the potential of biomarkers in combination with a disease-modifying treatment (DMT) can be revealed. However, such perfect test does not exist and estimating the accuracy for predicting the response of a hypothetical treatment is extremely difficult. A conventional economic evaluation which only compares a few alternative strategies would insufficiently reflect all possible values of diagnostic accuracy that CSF could have. The position of AD biomarkers in the clinical routine will nonetheless likely be either to verify AD in patients suspected of AD (which will cause increased sensitivity at the cost of specificity) or to rule-out AD (which will cause increased specificity at the cost of sensitivity, see Supplementary Fig. 2, available online). Exploring the consequences of these two strategies over their full range of possible accuracy values will provide insight in the potential value of biomarkers. The uprising application of AD biomarkers in practice urges the need for an early health technology assessment to explore future scenarios of a biomarker combined with a hypothetical DMT. This could aid in directing development and possible applications of AD biomarkers [7].

The aim of this early health technology assessment was to determine (1) the room of improvement of a perfect CSF biomarker and (2) the incremental net monetary benefit (NMB) of a CSF biomarker either in a strategy to verify an AD diagnosis or to rule-out an AD diagnosis as set by the current clinical practice diagnostic workup, compared with current clinical practice in MCI subjects under the condition that in all scenarios a hypothetical DMT for AD is available after diagnosis, from a societal perspective.

2. Methods

2.1. Design

A probabilistic patient-level model was used to synthesize available evidence on various disease components and simulate the difference in lifetime consequences of a group of individuals with MCI [8,9]. See the online Supplementary Material for a detailed description of all methods.

Evidence was mainly derived from the Dutch LEARN study including patients suspected of a primary neurodegenerative disease (NDD) [10], the Swedish Kungsholmen project which is a general population-based cohort from which incident MCI and incident dementia cases were filtered [11], the Dutch MEDICIE study on quality of life and resource utilization regarding a multidisciplinary diagnostic and management approach in psychogeriatric patients [12], literature, and expert opinion.

The room for improvement of a new technological intervention was defined as the benefit when the most optimistic plausible situation would be realized compared with current practice [13], that is, it assumes a perfect CSF test that is 100% sensitive and 100% specific. For the incremental NMB analysis (second aim) the strategy including a CSF biomarker in its diagnostic workup was compared with the current practice diagnostic workup without CSF. CSF was positioned in two alternative ways as an add-on test to the current clinical practice diagnostic workup that consisted of a physical, clinical, and neuropsychological examination, patient and informal caregiver history, and MRI, in MCI subjects who visited a memory clinic. First, the CSF test was performed only if the current practice workup concluded on the *presence* of AD (referred to as the "verify AD" strategy, that is, this prevented false positive diagnoses at the cost of false negatives; see Fig. 1 and Supplementary Fig. 2, and Supplementary Material Section 3.3); second, the CSF test was performed only if the current practice workup concluded on the *absence* of AD (referred to as the "rule-out AD" strategy, that is, this prevented false negative diagnoses at the cost of false positives; not presented in Fig. 1). In the control, headroom and both intervention strategies a hypothetical DMT was provided if AD was concluded from the strategy's diagnostic process. This was modeled as a one-time only treatment decision at incident MCI. The subject's lifetime costs and quality adjusted life years (QALYs) were compared between the current practice and each of the CSF strategies. Current available treatments (cholinesterase inhibitors and Memantine) were not modeled because they are not intended for people suffering from MCI [14].

Annual discount rates for costs and effects were set at 4% and 1.5%, respectively, according to the Dutch guideline for pharmacoeconomic research [15].

2.2. Model structure

An individual subject simulation model (see Fig. 1) was developed to model a population of 2000 incident MCI subjects (see Table 1) from a memory clinic setting. Each subject was quadruplicated; one went through the current practice control strategy and the other three went through the intervention strategies ("perfect test" for the room for improvement analysis, and the "verify AD" and "rule-out AD" for the incremental NMB analysis). If diagnosed with AD a hypothetical DMT was applied which, if diagnosed correctly, delayed conversion to dementia.

Disease progression in the dementia phase was modeled by the annual change in cognition (Mini-Mental State Examination or MMSE) and activity of daily living (ADL) (Katz score). Eventually the model stopped when the subject died or had been 30 years in the dementia phase. After completion and populating the model several quality checks were performed (see Supplementary Material Section 5.2).

2.3. Model assumptions

A subject's cause of MCI (AD, other NDD or no NDD) was assigned at the model start, and never changed because NDDs were considered nonreversible. All subjects with underlying AD or other NDD were considered at risk of developing the dementia syndrome. Subjects with no NDD when presenting at the memory clinic were assumed to never develop dementia. The hypothetical DMT only affected

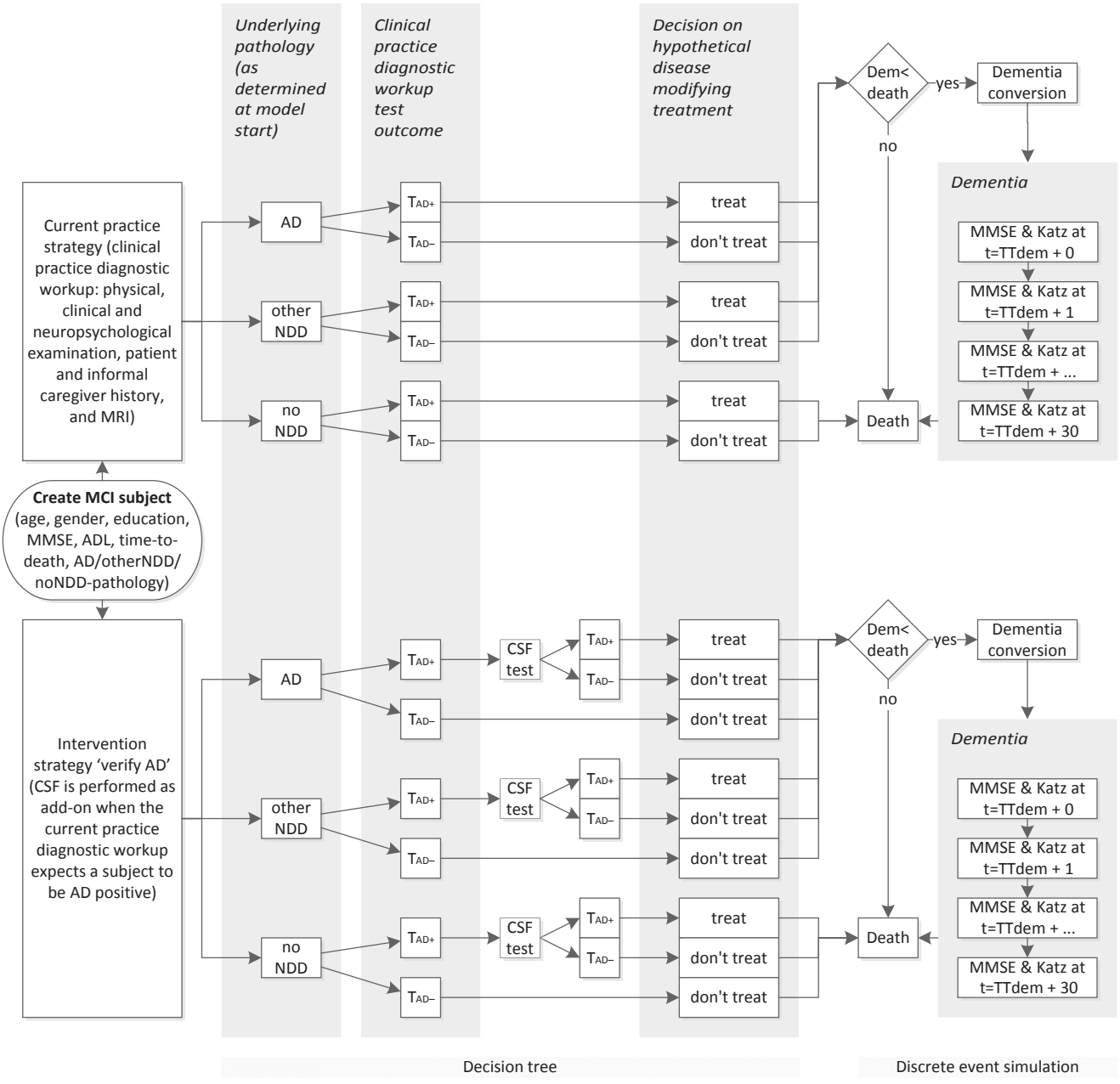

Fig. 1. General model structure for the incremental net monetary benefit analysis reflecting the current practice strategy and the "verify AD" strategy. The strategy 'rule-out AD' was not reflected. This strategy is identical to "verify AD", except that CSF is performed after clinical practice result T_{AD-} instead of T_{AD+}. The perfect test strategy for room for improvement analysis is identical to "verify AD", except that a perfect test is performed both after clinical practice T_{AD+} and after the T_{AD-} result. Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; Dem < death = the time to dementia conversion is estimated lower than the time to death; NDD, neurodegenerative disease; T_{AD+}, result of test workup indicates AD positive; T_{AD-}, result of test workup indicates AD negative; TTdem, time to dementia; t, time in years.

subjects with AD and was assumed to have no effect on survival. No (side effect) stopping rules were modeled.

2.4. Test-treat pathway

The diagnostic sensitivity and specificity of the current practice control strategy to predict hypothetical DMT response were assumed to be 77% and 68%, respectively. This was derived from the LEARN study as a best possible estimate using a clinical prognosis as index test and CSF beta-amyloid(1–42) total Tau ratio as a reference test (see Supplementary Material Section 3.3). Because of high uncertainty around this estimate a more generic approach that relaxes this point estimate assumption is explained later.

The diagnostic sensitivity and specificity of the intervention strategy to predict hypothetical DMT response was varied over multiple combinations of improved accuracy, which is explained later. Long-term disease progression could not

Table 1
Participant characteristics of the different data sources cohort studies and the simulated cohort

	MCI				Dementia	
Characteristic	Kungsholmen	MEDICIE	LEARN	Simulated cohort	Kungsholmen	MEDICIE
Number of measurements	153	57	58	2000	323	144
Age; mean (SD), range	83.4 (4.0), 76.3–97.7	74.9 (6.8), 55–87	68.4 (8.9), 50–89	68.3 (8.9), 37.9–94.7	86.7 (4.1), 78–100	78.7 (6.2), 60–94
Female; %	75%	53%	36%	36%	83%	73%
Years of education; mean (SD), range	8.5 (3.0), 3–16	N.A.	11.4 (3.5), 6–17	11.6 (3.4), 1–22.4	8.2 (2.9), 3–16	N.A.
MMSE; mean (SD), range	24.4 (2.1), 20–30	23.9 (4.3), 5–29	27.2 (2.2), 22–30	27.1 (2.0), 19.9–30	19.7 (5.0), 0–28	18.6 (5.5), 4–28
Katz; mean (SD), range	0.4 (0.7), 0–4	0.9 (0.7)*, 0–2.7	0.4 (0.8), 0–4	0.51 (0.56), 0–2.6	1.2 (1.7), 0–6	1.3 (0.7), 0–2.8

Abbreviations: MCI, mild cognitive impairment; SD, standard deviation; N.A., not applicable; MMSE, Mini-Mental State Examination.
*Katz is a surrogate Katz score based on the Lawton and the Disability Assessment for Dementia scale (see Supplementary Material Section 3.6).

be measured within the 2-year LEARN project and was therefore assessed in the Swedish Kungsholmen project, a general population-based cohort design with 6-year follow-up after incident MCI or incident dementia [11]. The time to death was sampled from the 2012 survival table from the Dutch national central bureau for statistics.

A hypothetical constant treatment effect of 50% progression reduction was applied on the time from MCI to dementia conversion, and on the rate of cognitive (MMSE) and ADL (Katz score) decline which was based on similar assumptions on hypothetical DMT efficacy found in the literature [16].

2.5. Costs and health utilities

Cost data were analysed from 1-year resource use interview data of 201 participants from the MEDICIE study [12,17] (see Supplementary Material Section 3.7). In summary predictors of 1-year care costs were estimated separately for MCI and dementia patients.

The costs in MCI were determined by the Katz score, whereas Katz and MMSE were the drivers of the costs in dementia patients. The costs of the CSF biomarker per individual were estimated €211 ($272) based on expert opinion. Treatment costs were estimated to be €5853 ($7550) per individual per year based on the assumptions provided by Sköldunger et al. [16]. All costs were expressed in Euros at 2012 values (at that time, €1.00 was equivalent to US $1.29 and British £0.81).

Similar to the cost analyses, health-related quality of life analyses were performed using the Maastricht Evaluation of a Diagnostic Intervention for Cognitively Impaired Elderly (MEDICIE) data EQ-5D utility scores [12]. Utilities reflect the desirability of a health state, measured from 1 (representing perfect health) to 0 (representing death). Similar to the cost analyses gender, age, MMSE, a Katz surrogate scale, and all two-way interactions were tested in a backward regression ($P < .05$). Utility in MCI was determined by the Katz score, whereas it was determined by gender, MMSE, Katz, and the interaction between gender and MMSE in dementia patients.

Individual disutility due to DMT side effects was estimated by expert opinion (FV) at a constant 0.05 as long as the treatment was provided. The nonmedical consequences of an incorrect prognosis of dementia were assumed to be caused by coping with personal decisions such as incorrect future care planning that was made based on the wrong information. The disutility of an incorrect AD positive diagnosis was estimated to be 0.25 for 1 year and for an incorrect AD negative diagnosis 0.15 for 1 year by expert opinion (FV).

2.6. Outcome measures

The primary outcome measures were the lifetime average costs and QALYs over the 2000 individually simulated subjects. These were calculated for both the current practice control strategy and the strategy of a perfect biomarker test and aggregated into a single net monetary benefit. QALYs were multiplied by the maximum Dutch willingness to pay €80,000 [18] ($103,200) per QALY to express them in monetary terms.

2.7. Output representation

As explained in the introduction the predictive accuracy of CSF is unknown and was therefore ranged over all plausible values. The incremental NMB estimates for each combination of sensitivity and specificity were averaged and plotted in a three-axes graph (Fig. 2A). In this graph the horizontal and depth axis represent a receiver operating characteristic plane. The combination of 77% sensitivity and 68% specificity represented the current practice situation and a set of plausible combinations (see Supplementary Material Section 3.3) of sensitivity and specificity (see Supplementary Material Section 3.11) was used to represent the "verify AD" strategy. Next, an interpolation line was drawn through the sensitivity and specificity combinations at which the incremental NMB was zero. This represents the minimally required level of sensitivity and specificity to ensure cost-effective use of the CSF intervention when it is used to "verify AD". An identical method was used for the "rule-out AD" strategy represented by Fig. 3A.

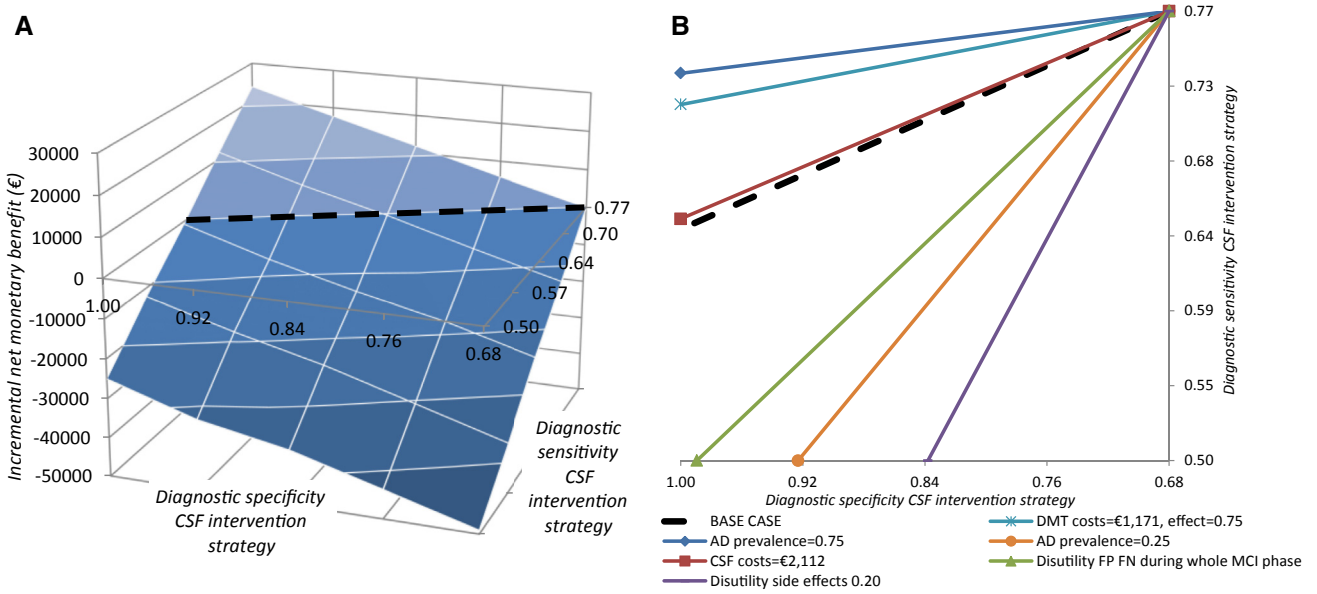

Fig. 2. (A) Left: Incremental net monetary benefit (NMB, €) of the "verify AD" strategy (i.e., a CSF test was performed if the current practice diagnostic workup was AD *positive*). The incremental NMB was drawn in a Receiver Operator Characteristic plane for each combination of sensitivity (ranging from 0.50 to 0.77) and specificity (ranging from 0.68 to 1) at a willingness to pay of €80,000 ($103,200). (B) Right: Results of varying the fixed parameters in a univariate sensitivity analysis relative to the base case scenario. The base case scenario consisted of DMT costs = €5853 ($7553) and DMT efficacy = 0.5, AD prevalence = 49%, CSF costs = €211 ($272), disutility FP and FN only first MCI year, DMT side effects disutility = 0.05. The dotted black line in the left and right graph represents the specific combinations of minimal diagnostic sensitivity and specificity at which the CSF intervention was cost-effective in the base case scenario and thus had a positive incremental NMB. These dotted lines correspond to each other in both graphs. Abbreviations: NMB, net monetary benefit; AD, Alzheimer's disease; CSF, cerebrospinal fluid; DMT, disease-modifying treatment; FP, false positive; FN, false negative; MCI, mild cognitive impairment.

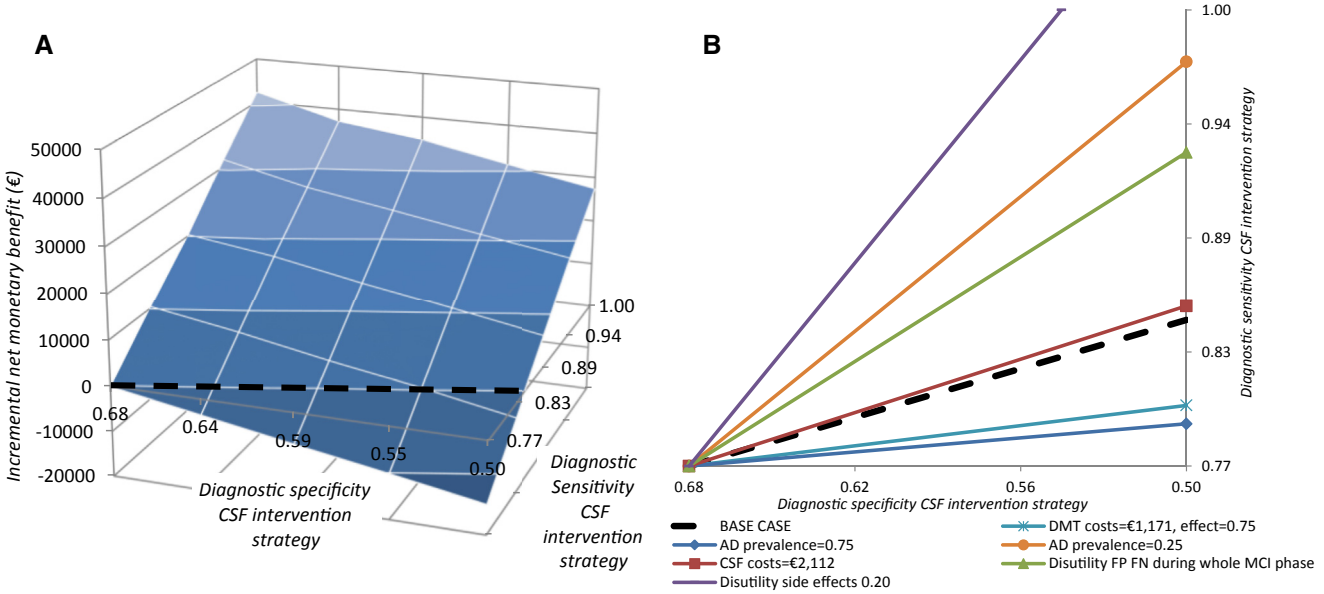

Fig. 3. (A) Left: Incremental net monetary benefit (NMB, €) of the "rule-out AD" strategy (i.e., a CSF test was performed if the current practice diagnostic workup was AD *negative*). The incremental NMB was drawn in a Receiver Operator Characteristic plane for each combination of sensitivity (ranging from 0.77 to 1) and specificity (ranging from 0.50 to 0.68) at a willingness to pay of €80,000 ($103,200). (B) Right: Results of varying the fixed parameters in a univariate sensitivity analysis relative to the base case scenario. The base case scenario consisted of DMT costs = €5853 ($7553) and DMT efficacy = 0.5, AD prevalence = 49%, CSF costs = €211 ($272), disutility FP and FN only first MCI year, DMT side effects disutility = 0.05. The dotted black line in the left and right graph represents the specific combinations of minimal diagnostic sensitivity specificity at which the CSF intervention was cost-effective in the base case scenario and thus had a positive incremental NMB. These dotted lines correspond to each other in the both graphs. Abbreviations: NMB, net monetary benefit; AD, Alzheimer's disease; CSF, cerebrospinal fluid; DMT, disease-modifying treatment; FP, false positive; FN, false negative; MCI, mild cognitive impairment.

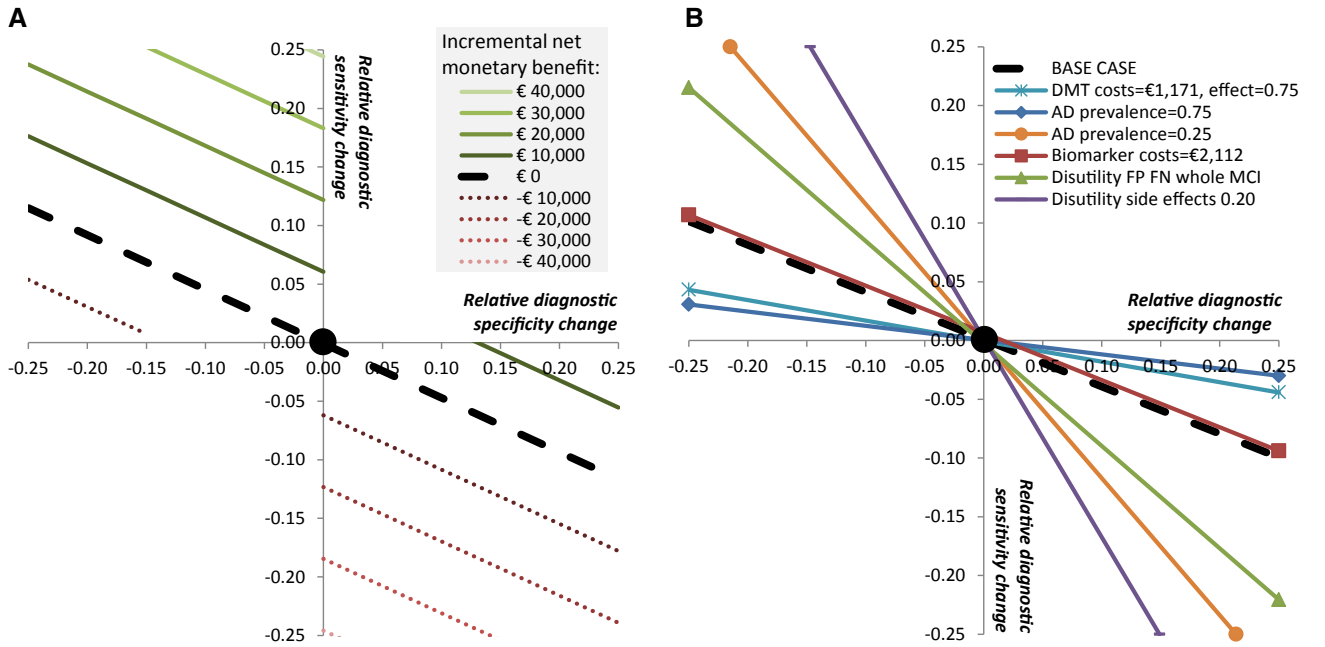

Fig. 4. (A) Left: Incremental NMB (€) of (1) the intervention strategy where a biomarker was performed if the current practice diagnosis was AD *positive* (verify AD) in the bottom right quadrant and (2) the intervention strategy where a biomarker was performed if the current practice diagnosis was AD *negative* (rule-out AD) in the left top quadrant. The black dot represents the current practice diagnostic situation (i.e., control strategy). The axes present the relative sensitivity and specificity change of predicting DMT response due to an AD biomarker relative to current practice. The right top represents a situation with both improved sensitivity and improved specificity, the left bottom quadrant represents both decreased sensitivity and decreased specificity. These scenarios fell outside the scope of this article. (B) Right: Results of varying the fixed parameters from the base case scenario (base case DMT costs = €5853 ($7553) and DMT efficacy = 0.5, AD prevalence = 49%, biomarker costs = €211 ($272), disutility FP and FN only first MCI year, DMT side effects disutility = 0.05) in a univariate sensitivity analysis. The intervention strategy is cost-effective at all combinations of sensitivity and specificity at the right top area of each line, and not cost-effective at the left bottom area of each line. The dotted black lines in the left and right graph represent the specific combinations of minimal sensitivity and minimal specificity at which the biomarker intervention was cost-effective in the base case scenario and thus had at a positive incremental NMB. These lines correspond to each other. Abbreviations: NMB, net monetary benefit; AD, Alzheimer's disease; DMT, disease-modifying treatment; FP, false positive; FN, false negative; MCI, mild cognitive impairment.

Because even the accuracy of current practice in terms of sensitivity and specificity is highly uncertain, a more generic graph was built in Fig. 4. It relies on the relative accuracy change (from current practice sensitivity and specificity to the "verify AD" intervention or to the "rule-out AD" sensitivity and specificity) instead of absolute accuracy values. The generated results can be applied in any situation of control versus intervention accuracy estimates for any biomarker in AD under the condition that DMT is available. This Fig. 4 represents incremental NMB isoquants by incremental changes in sensitivity and specificity, where 0% to 25% increase in specificity was at the cost of −25% to 0% decrease in sensitivity for the "verify AD" relative to the current practice control strategy, and 0% to 25% increase in sensitivity was at the cost of −25% to 0% decrease in specificity for the "rule-out AD" relative to the current practice control strategy.

2.8. Uncertainty analyses

In a probabilistic sensitivity analysis, the simulation of the same 2000 subjects was run 10,000 times using sets of random parameter values that were drawn to reflect parameter uncertainty generating 95% credibility intervals (CI) based on the 2.5 and 97.5 percentile of the 10,000 simulations (see Supplementary Material Section 4.1).

In univariate sensitivity analyses of the room for improvement the outcomes (i.e., incremental differences between the control strategy and both intervention strategies) was calculated for scenarios different from the base case by running the simulation using 2500 iterations for each scenario (see Supplementary Material Section 4.2). First, a more efficient treatment (DMT costs = €1171 [$1511]; DMT efficacy = 0.75) and a less efficient treatment (DMT costs = €35,119 [$45,304]; DMT efficacy = 0.25) were evaluated using the same estimates as used in the sensitivity analysis of Sköldunger et al. [16]. Next, the outcomes were calculated for the scenario of a high AD prevalence (75%) and a low prevalence (25%) estimate. At last, the scenarios of 10-folded CSF costs (€2112 ($2724)), longer disutility of the nonmedical consequences (disutility of a false positive [FP] and false negative [FN] diagnosis lasted during whole MCI phase), and higher disutility of DMT side effects (0.20) were separately evaluated. These estimates were based on expert opinion (FV) since in this early stage of Health Technology Assessment likely estimates were unknown.

The univariate sensitivity analyses of the "verify AD" and "rule-out AD" strategies are presented by Figs. 2B and 3B, respectively. By taking other scenarios (the same as described previously) the specific combinations of sensitivity and specificity at which the CSF was cost-effective to "verify AD" or "rule-out AD" changed. This was expressed by a shift from the dotted black line (that represents the base case conditions) to the plain colored lines that represent each of the sensitivity analyses conditions.

3. Results

The 2000 simulated MCI subjects had an average (SD) age of 68.3 (8.9), female proportion of 36%, MMSE of 27.1 (2.0), Katz of 0.51 (0.56), and 49% suffered from AD pathology. In the current practice, control strategy subjects had on average (95% CI) 8.67 (7.84–9.47) QALYs and consumed care resources worth €545,712 (465,746 to 636,095) ($703,968). The room for improvement analysis revealed 0.39 (0.26–0.54) additional QALYs and €33,622 (21,232 to 50,780) ($43,372) savings on average per subject if a perfect test existed (from 77% sensitivity and 68% specificity in the control strategy (i.e., current practice diagnostic workup without CSF) for predicting a hypothetical DMT response to 100% sensitivity and 100% specificity in the perfect CSF test strategy for predicting a hypothetical DMT response); this resulted in an incremental NMB of €64,940 (43,995–90,755) ($83,773). Secondary outcome measures revealed 2.0 (1.7–2.3) additional potential beneficial treatment years and dementia conversion occurred 1.3 (1.0–1.7) years later than the current practice control strategy.

Figs. 2A and 3A represent the incremental NMB of each combination of sensitivity and specificity for the "verify AD" and the "rule-out AD" strategies, respectively, compared with the current practice control strategy.

3.1. Univariate sensitivity analysis

The results of the univariate sensitivity analyses on the room for improvement are presented in Table 2. The incremental NMB of both the current practice and the perfect test strategy was highest under the condition of a more efficient treatment.

The high and low AD prevalence conditions in the univariate sensitivity analyses on the room for improvement analysis (Table 2) had only a minor effect on the costs and QALYs in the base case situation. This can be explained by the fact that not all subjects with AD survived up to the point of dementia conversion and thus had not benefit from treatment. Furthermore, a lower prevalence of AD implicated an increase of other NDDs (see Supplementary Table 9) for which treatment was ineffective. This increased the care resources required for dementia care. Figs. 2B and 3B represent the sensitivity analyses of the incremental NMB of the "verify AD" and "rule-out AD" strategies. They show that a lower AD prevalence, a longer disutility due to incorrect diagnoses, and a higher DMT side effect's disutility increased the range of sensitivity and specificity combinations for which CSF was cost-effective in the "verify AD" strategy. These scenarios decreased the range of combinations for which CSF was cost-effective in the "rule-out AD" strategy. For the other analyses (more efficient DMT and high AD prevalence) this was vice versa. Increased CSF costs slightly decreased the number of cost-effective combinations. If DMT was less efficient the "verify AD" strategy was cost-effective for all combinations of increased specificity and decreased sensitivity, and the "rule-out AD" strategy was never cost-effective. These various sensitivity analyses changed the optimal position of the CSF test due to a shift in the balance between benefits of preventing over- and undertreatment. For example, in case of a lower AD prevalence the number of subjects with overtreatment increased which emphasizes the importance of a high test specificity to prevent this and keep DMT provision cost-effective (i.e. the forgone resources and QALY loss due to overtreatment in a large part of the population were not compensated for by the benefits of preventing undertreatment of a small part of the population).

Fig. 4 is similar to Figs. 2 and 3 and presents the situation of a relative change in sensitivity and specificity due to a generic biomarker intervention compared with the current practice situation for both the "verify AD" in the right bottom quadrant and "rule-out AD" in the left top quadrant of the graph.

4. Discussion

The incremental costs and QALYs between the control strategy and a perfect test to reveal the room for improvement and between the control strategy and two strategies in which a CSF biomarker was added to the current clinical practice diagnostic workup (either to verify an AD diagnosis or a no-AD diagnosis) were estimated by a decision model for MCI assuming a hypothetical DMT was available. The analysis indicated a room for improvement of 0.39 (0.26–0.54) QALYs gained and €33,622 (21,232–50,780) ($43,372) savings on average per subject if a perfect test existed compared with current practice. The strategy that used CSF to rule-out AD as set by the current clinical practice diagnostic workup indicated more potential benefit than the strategy that used CSF to verify AD, given the assumptions on a hypothetical DMT effect. This implies that if such DMT becomes available, biomarker research should focus on improving the specificity of a test. Also, this study emphasizes that the full test-treatment pathway should be considered in biomarker research because it is mainly not the test itself that improves patient-important outcomes but the downstream management [19].

Table 2
Mean individual lifetime primary and secondary outcome estimates (based on 2500 model iterations) of the sensitivity analyses of the current practice control strategy (current practice diagnostic workup without CSF [=cur]) and headroom (CSF test in addition to current practice's diagnostic workup with 100% sensitive and 100% specific [=room]), both under the condition of hypothetical DMT

	Costs (k€ (k$))		QALYs		NMB (k€ (k$))		Conversion age		Beneficial treatment years		Incremen-tal
	Cur	Room	Cur	Room	Cur	Room	Cur	Room	Cur	Room	NMB (k€ (k$))
Base case*	546 (704)	512 (660)	8.7	9.1	148 (191)	213 (275)	81.1	82.4	6.6	8.6	65 (84)
More efficient treatment†	491 (633)	452 (583)	8.9	9.4	223 (288)	299 (386)	89.8	93.7	6.6	8.6	76 (98)
Less efficient treatment‡	777 (1002)	741 (956)	8.2	8.4	−122 (−157)	−66 (−85)	78.2	78.6	6.6	8.6	56 (72)
High AD prevalence (75%)	548 (707)	508 (655)	8.7	9.1	144 (186)	219 (283)	82.2	83.8	10.1	13.1	75 (96)
Low AD prevalence (25%)	540 (697)	512 (660)	8.8	9.1	161 (208)	218 (281)	79.7	80.5	3.5	4.6	56 (73)
High CSF costs (€2112)	546 (704)	514 (663)	8.7	9.1	148 (191)	211 (272)	81.1	82.4	6.6	8.6	63 (81)
Longer disutility FP/FN§	548 (707)	514 (663)	8.1	9.1	99 (128)	211 (272)	81.1	82.4	6.6	8.6	112 (145)
High disutility DMT (0.20)	546 (704)	512 (660)	7.5	8.0	53 (68)	126 (163)	81.0	82.3	6.6	8.6	74 (95)

Abbreviations: CSF, cerebrospinal fluid; DMT, disease-modifying treatment; QALY, quality adjusted life years; NMB, net monetary benefit; AD, Alzheimer's disease; FP/FN, false positive/false negative.

*Base case analysis: Annual individual DMT costs = €5855 ($7553); DMT efficacy = 0.5; AD prevalence = 49%; individual CSF costs = €211 ($272); individual disutility FP = .25 only in the first year; disutility FN = 0.15 only in the first year; disutility side effects = 0.05.

†DMT costs = €1171 ($1511); DMT efficacy = 0.75.

‡DMT costs = €35,119 ($45,304); DMT efficacy = 0.25.

§Disutility of the nonmedical consequences of a FP and FN diagnosis is during the whole mild cognitive impairment phase.

The reason for the larger potential benefit of the "rule-out AD" strategy is due to the treatment benefits in subjects with AD. In a post-hoc analysis we retrospectively filtered the simulated subjects who had AD although were not diagnosed as such by the current practice control strategy but who were correctly diagnosed as AD by the CSF test and treated accordingly (i.e., undertreatment was prevented by CSF). On average these subjects gained 2.04 (0.90–3.34) QALYs and €201,099 (93,555–347,341) ($259,418) savings during lifetime. This was much higher than the benefits for preventing overtreatment as revealed by a post-hoc analysis (i.e., wrongly diagnosed as AD and thus unnecessarily treated with DMT by the current practice and correctly diagnosed as non-AD due to the CSF test in the intervention strategy) which were 0.99 QALYs (0.95–1.03) gained and €67,536 savings (64,409–70,594) ($87,121). The potential benefit in untreated AD subjects reflects the high demand on care resources in dementia, which has been estimated between €6614 ($8532) and €64,426 ($83,110) per year per person [17,20]. In the decision model DMT diminished the dementia care by postponing dementia conversion which saved more care usage costs than the assumed costs to operationalize DMT itself.

Other studies have evaluated the cost-effectiveness of hypothetical DMT combined with an AD biomarker in MCI subjects. Sköldunger et al. [16] found that DMT was more cost-effective in a population enriched with more treatment responders. They extensively elaborated on DMT scenarios and the impact of mortality on cost-effectiveness but evaluating diagnostic strategies was not their goal. Biasutti et al. [21] showed that MRI with contrastophore–linker–pharmacophore in combination with a hypothetical DMT available at €1144 ($1476) per year was cost-effective. A similar result was found by Guo et al. [22] for florbetaben PET. The latter study included the consequences of a reduced time to confirmed diagnosis on a delay of institutional care. Our study estimated the CSF's room for improvement and explicitly positions the CSF biomarker as an add-on clinical practice test to verify or rule-out AD.

4.1. Strengths and limitations

The model's major strengths included explicitly positioning the CSF diagnostic marker in the current clinical diagnostic workup and using input evidence that was based on long-term progression observations. The model was subject to several limitations. The not knowing of several parameters is inherent to this early assessment of technologies. For this reason we deviated from the conventional method of comparing a limited number of alternative strategies and evaluated any combination of the CSF intervention's test sensitivity and specificity. It enabled us to show the most optimal position of a new AD biomarker under various predefined conditions.

The diagnostic process in all strategies was simplified by not taking into account the time between a first memory clinic visit and the final diagnosis, a possible false or undetermined diagnosis, time to rediagnosis, and the time to a next doctor visit after dementia conversion. These aspects are, however, of secondary relevance to the explorative nature of this analysis. Lumbar puncture (headache) side effects were not taken into account. DMT was simplified by not taking willingness to receive treatment, stopping rules due to side effects, or the effect of age on treatment efficacy into account. The effect of DMT on survival was

not modeled because it has a complex interaction with cost-effectiveness, which has been extensively researched by Sköldunger et al. [16]. This resulted in a small proportion (1.6%) surviving dementia for more than 30 years, which is a limitation of the lifetime generalizability to the real-world.

The discretization and the truncation of the polynomial disease progression formulas simplified the long-term predictions and ensured generalizability. Also, the transformation of the Disability Assessment for Dementia scale to a Katz surrogate score using the Lawton scale most likely generates uncertainty to how well they reflect the actual estimates. The possible error of these simplifications is identical in both the control and intervention strategies, although if the Katz transformation led to an overestimation of its scores, it amplified the Katz related care costs in dementia, which had a higher rate of conversion in the control strategy. The impact on the conclusions was judged small.

Resource use and utility scores were obtained from a clinical sample and disease progression from a general population-based sample. Memory clinic subjects are likely to have more severe problems at diagnosis because the complaint must be severe enough to initiate a visit. This might underestimate the CSF benefits because these subjects miss a window of opportunity for early treatment.

The nonmedical consequences of an early diagnosis on quality of life were unknown and estimated by expert opinion. Even if the true value is unknown, it has been emphasized [23] to include such uncertain estimates. For example, a related study by McMahon et al. [24] in demented subjects has included an assumed decrease in quality of life of 0.05 utility score due to a false diagnosis.

5. Conclusions

CSF and related AD biomarkers have the potential to increase care efficiency when DMT becomes available. The incremental NMB analysis indicated more potential benefit from a biomarker that was positioned to verify subjects who are not expected to have AD (i.e., a treatment selection approach to prevent undertreatment) rather than to verify subjects expected of AD (a treatment selection approach to prevent overtreatment) given the assumptions on a hypothetical DMT.

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Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.jalz.2015.02.009.

RESEARCH IN CONTEXT

1. Systematic review: Economic evaluations of diagnostic techniques have been reviewed by Handels et al. [5]. We updated this review focussing on cerebrospinal fluid (CSF) and did not retrieve additional studies. Related studies in positron emission tomography and magnetic resonance imaging were used to compare our results to.
2. Interpretation: Similar to other studies we estimated the potential of biomarkers assuming a hypothetical disease modifying treatment is available. In addition to previous studies we explicitly positioned CSF in the current clinical diagnostic workup and showed that a strategy of ruling out a clinical diagnosis of Alzheimer's disease (AD) indicated more potential benefit than a strategy of verifying AD, given the assumptions on the hypothetical treatment.
3. Future directions: To expand our findings the nonmedical consequences of diagnostic testing should be estimated. This would allow estimating the value of CSF in current practice mild cognitive impairment subjects, without available disease modifying treatment and recommend on the position of CSF in the current diagnostic workup.

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