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Using Cerebrospinal Fluid Biomarker Testing to Target Treatment to Patients with Mild Cognitive Impairment: A Cost-Effectiveness Analysis

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Abstract

Objective Cerebrospinal fluid (CSF) biomarkers are shown to facilitate a risk identification of patients with mild cognitive impairment (MCI) into different risk levels of progression to Alzheimer's disease (AD). Knowing a patient's risk level provides an opportunity for earlier interventions, which could result in potential greater benefits. We assessed the cost effectiveness of the use of CSF biomarkers in MCI patients where the treatment decision was based on patients' risk level.

Methods We developed a state-transition model to project lifetime quality-adjusted life-years (QALYs) and costs for a cohort of 65-year-old MCI patients from a US societal perspective. We compared four test-and-treat strategies where the decision to treat was based on a patient's risk level (low, intermediate, high) of progressing to AD with two strategies without testing, one where no patients were treated during the MCI phase and in the other all patients were treated. We performed deterministic and probabilistic sensitivity analyses to evaluate parameter uncertainty.

Results Testing and treating low-risk MCI patients was the most cost-effective strategy with an incremental cost-effectiveness ratio (ICER) of US\$37,700 per QALY. Our results were most sensitive to the level of treatment effectiveness for patients with mild AD and for MCI patients. Moreover, the ICERs for this strategy at the 2.5th and 97.5th percentiles were US\$18,900 and US\$50,100 per QALY, respectively.

Conclusion Based on the best available evidence regarding the treatment effectiveness for MCI, this study suggests the potential value of performing CSF biomarker testing for early targeted treatments among MCI patients with a narrow range for the ICER.

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Key Points for Decision Makers

Treating MCI patients at low risk generated greater benefits, although it may be counterintuitive.

With a high degree of uncertainty, the decision of whether to treatment MCI patients or not based on their risk levels may benefit from gathering more information on the treatment effectiveness for MCI.

1 Introduction

Alzheimer's disease (AD) is a devastating neurodegenerative disease that impairs memory, thought, and behavior; reduces quality of life; and decreases survival. As more people live long enough to become at-risk [1, 2], identifying patients early in the disease continuum for greater benefits from the potential interventions may alleviate some of the burden on patients, caregivers, and society [3, 4].

Prior to AD diagnosis, most patients progress through a prodromal stage called mild cognitive impairment (MCI) [5], which is a stage characterized by early memory loss but with relatively well-preserved activities of daily living. On average, MCI patients face a 10–15% risk of progression to AD each year [5–10]. Identifying patients at risk for progression to AD at an earlier stage provides an opportunity to make decisions about disease management plans and financial arrangements while cognitive function is still capable [11, 12], and to access interventions with disease-modifying effects if they were to become available [13, 14].

Cerebrospinal fluid (CSF), consisting of a concentration of $A\beta_{1-42}$ (a biomarker of amyloid β deposition in the brain), total tau, and phosphorylated tau proteins [15, 16], are shown to facilitate the identification of MCI patients who are at different risk levels of progression to AD [13, 17–19] and are included in the currently proposed diagnostic criteria for AD [13] and MCI [20]. Moreover, they are also considered the most preferred biomarkers for studying disease progression due to their unique clinical features and low incidences of complications [21, 22]. Accordingly, several multidisciplinary working groups have either recommended using CSF biomarkers in the diagnostic workup of MCI patients [23] or proposed the utilization of CSF biomarkers in informing the likelihood of the progression to AD among MCI patients [4, 24].

There is currently no cure for AD. With a hypothetical disease-modifying therapy (DMT), however, data from several simulation models supported the benefits of early identification at the prodromal or predementia stage using various diagnostic tools such as florbetaben positron emission tomography [25], brain magnetic resonance imaging [26], apolipoprotein $\epsilon 4$ genetic test [27], or CSF biomarkers [28, 29]. In addition, some models compared the strategy of a DMT versus the strategy of no DMT in patients with MCI (the decision to treat or not was not based on the testing results) [30, 31]; others compared different diagnostic strategies with these novel testing techniques as an add-on to standard diagnostic procedures [25, 26, 28].

The potential value of these tools to facilitate the detection of AD at an early phase is only considered

speculative [14] due to the scant evidence pertaining to the effectiveness of existing treatments for MCI patients. Yet, results of a randomized clinical trial (RCT) [32] and meta-analysis studies [33–37] showed the potential benefits of cholinesterase inhibitors (ChEIs; e.g., donepezil, galantamine, and rivastigmine) to delay the progression from MCI to AD. Additionally, it is suggested by the recent revision of cost-effectiveness analysis (CEA) recommendations [38] that if a decision must be made (in our case whether or not to intervene for MCI patients based on their CSF biomarker test results), it should be made based on the data availability. Given the clinical utility of CSF biomarkers and the best available data on treatment effectiveness, therefore, the objective of our study was to determine the potential value of the use of CSF biomarker testing in MCI patients by comparing various test-and-treat strategies with strategies without test information. Here, CSF biomarkers were used as a risk-stratification tool to categorize patients into different risk levels of progression to AD (instead of a diagnostic tool to dichotomize patients into positive or negative testing results), and the decision to treat was based on a patient's risk level.

2 Methods

We developed a state-transition model to estimate the costs, quality-adjusted life-years (QALYs), and cost effectiveness of performing one-time CSF biomarker testing for a cohort of 65-year-old MCI patients and then treating some of these patients with ChEIs based on their biomarker test results. We used evidence from a primary data analysis [19] and the published literature to derive relevant parameters. Costs and health outcomes were discounted 3% annually per the US recommendation [39], and the model cycle length was 1 year. We adopted a US societal perspective and a lifetime horizon.

2.1 Model Structure

Figure 1 illustrates the model structure. MCI patients who undergo biomarker testing are assigned a high-, intermediate-, or low-risk score that determines their risk of progressing to AD [19]. On the basis of this score, a subset of patients would be treated with ChEI therapy in the MCI stage. Providing treatment in this phase introduces a cost and imposes a risk of experiencing side effects but also might reduce a patient's risk of developing AD. If MCI patients progress to AD, whether treated or not, they progress through a series of health states defined by AD severity (mild, moderate, or severe) and residential settings (community or nursing home). Each year, patients are

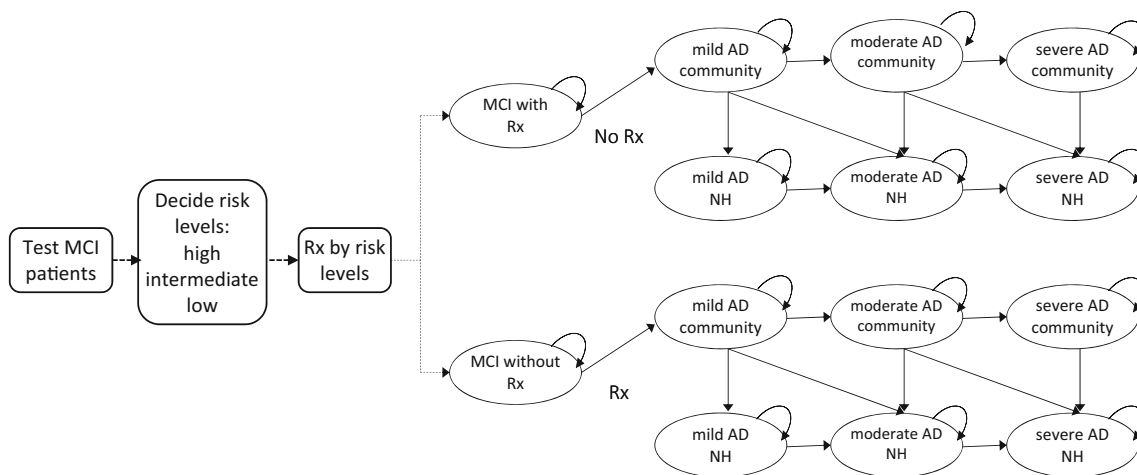


Fig. 1 Schematic diagram of CSF biomarker testing and subsequent treatment for patients with MCI. AD Alzheimer’s disease, CSF cerebrospinal fluid, MCI mild cognitive impairment, NH nursing home, Rx treatment

allowed to transition to another health state (progress in severity or transition to nursing home), remain in the same health state, or die. Once AD patients enter a nursing home we assumed that they would remain in the institution until death [40], given that most patients entering the nursing home have severe AD.

2.2 Treatment Strategies

Because MCI patients could be categorized into one of three risk levels of progression to AD based on their CSF biomarker testing results (a positive and ordinal relationship), we evaluated six test-and-treat strategies as follows:

1. *No testing and no MCI treatment* Treat only when MCI patients convert to AD and stop treatment when they progress to the severe stage.
2. *Test and treat high risk* Test MCI patients and only treat those with a high-risk result until AD conversion; no treatment for low- and intermediate-risk patients until they convert to AD and stop treatment when they progress to the severe stage.
3. *Test and treat high or intermediate risk* Test MCI patients and treat those with a high- or intermediate-risk result until AD conversion; no treatment for low-risk patients until they convert to AD and stop treatment when they progress to the severe stage.
4. *Test and treat low risk* Test MCI patients and treat those with a low-risk result until AD conversion; no treatment for high- and intermediate-risk patients until they convert to AD and stop treatment when they progress to the severe stage.
5. *Test and treat low or intermediate risk* Test MCI patients and treat those with a low- or intermediate-risk result until AD conversion; no treatment for high-risk

patients until they convert to AD and stop treatment when they progress to the severe stage.

6. *No testing and treat all MCI patients* Treat all MCI patients and stop treatment when patients convert to AD.

Because evidence on the treatment effectiveness for MCI patients is indefinite, we assumed that if MCI patients received treatment, they would not be eligible for ChEI treatment if they converted to AD based on clinical expert opinion. We tested this assumption in the sensitivity analysis.

2.3 Model Parameters

Table 1 summarizes the parameter estimates and their 95% confidence intervals (CIs) if available. Otherwise, we used 50% higher or lower than the mean as the upper bound and lower bound for the parameter estimate [41].

2.3.1 Disease Progression

In previous work [19], we estimated annual transition probabilities from MCI to AD for each risk group (high, intermediate, and low) defined by CSF biomarker levels using 6-year follow-up data from the Alzheimer’s disease Neuroimaging Initiative with 195 MCI patients. In brief, time-dependent receiver operator characteristic analysis was used to choose the best combination of CSF biomarkers on the longitudinal predictive ability for the progression of AD for MCI patients. Baseline CSF biomarker levels were summarized into a multi-biomarker score by multiplying the biomarker level with each of their own coefficients $([-0.006] \times A\beta_{1-42} + 0.012 \times P\text{-tau}_{181p})$ [19], derived from the fitted Cox proportional

Table 1 Parameter inputs for the state-transition model

Parameter	Mean	95% CI	Distribution	Source
Annual probability of progression from MCI to AD by CSF biomarker score ^a				[19]
Low-risk group	0.064	0.01–0.16	Beta (2.46, 35.93)	
Intermediate-risk group	0.108	0.03–0.22	Beta (4.05, 33.48)	
High-risk group	0.244	0.17–0.33	Beta (27.89, 86.40)	
Prevalence of MCI patients by risk levels				[19]
Low-risk group	0.6			
Intermediate-risk group	0.2			
High-risk group	0.2			
Annual transition probability				[40, 79]
Stage to stage (AD)				
Mild to moderate	0.167	0.156–0.178	Beta (690.43, 3443.86)	
Mild to severe	0.014	0.010–0.018	Beta (59.63, 4199.86)	
Moderate to severe	0.299	0.286–0.312	Beta (1355.02, 3176.83)	
Community to nursing home				
Mild AD	0.012	0–0.028	Beta (2.27, 186.70)	
Moderate AD	0.034	0–0.069	Beta (3.57, 101.46)	
Severe AD	0.066	0.005–0.128	Beta (3.74, 52.91)	
Excess mortality due to AD (additive effect) ^b	0.11	0.055–0.165		[53, 54]
Treatment effectiveness (RR)				
MCI patients	0.84	0.70–1.02	Lognormal (–0.17, 0.096)	[36]
AD patients				
Mild to moderate	0.58	0.35–0.76	Lognormal (–0.55, 0.198)	Estimated by authors
Moderate to severe	0.95	0.64–1.41	Lognormal (–0.05, 0.114)	[42]
Treatment harm				
Annual prob. of AE (control)	0.23	0.2–0.26	Beta (173.78, 581.77)	[43]
AEs in MCI (RR)	1.09	1.02–1.16	Lognormal (0.086, 0.033)	[36]
AEs in AD (RR)	2.09	1.81–2.40	Lognormal (0.736, 0.073)	[44]
Withdrawal due to AE ^c	0.18	0.13–0.22	Beta (41.67, 181.76)	[44]
Withdrawal due to non-AE in MCI	0.046	0.035–0.058	Beta (52.94, 1201.7)	Assumed
Withdrawal due to non-AE in AD	0.11	0.10–0.12	Beta (190.03, 1543.9)	Assumed
Health utility				
MCI	0.73	0.58–0.88	Beta (23.86, 8.82)	[27, 80]
AD				[49]
Mild				
Community	0.68	0.54–0.82	Beta (28.34, 13.34)	
Nursing home	0.71	0.57–0.85	Beta (27.97, 11.42)	
Moderate				
Community	0.54	0.43–0.65	Beta (42.08, 35.85)	
Nursing home	0.48	0.37–0.59	Beta (37.59, 40.72)	
Severe				
Community	0.37	0.29–0.45	Beta (67.3, 114.6)	
Nursing home	0.31	0.24–0.38	Beta (51.72, 115.11)	
AE ^d	0.95	0.916–0.976	Beta (190, 10)	[29]
Lumbar puncture ^d	0.01	0.009–0.012	Beta (9800, 99)	Assumed, [52]
Cost (US\$, per person-year)				
MCI	7467	3733–11,200	Gamma (15.36, 0.0021)	[56]
Formal				[55]
Mild AD				

Table 1 continued

Parameter	Mean	95% CI	Distribution	Source
Community	9380	4690–14,070	Gamma (15.37, 0.0017)	
Nursing home	50,865	25,432–76,297	Gamma (15.37, 3.06)	
Moderate AD				
Community	13,859	6929–20,788	Gamma (15.37, 0.0011)	
Nursing home	55,362	27,681–83,043	Gamma (15.37, 2.81)	
Severe AD				
Community	20,889	10,445–31,334	Gamma (15.37, 7.46)	
Nursing home	59,327	29,664–88,991	Gamma (15.37, 2.63)	
Informal				[55]
Mild AD				
Community	11,876	5938–17,815	Gamma (15.37, 0.0013)	
Nursing home	1267	633–1900	Gamma (15.33, 0.0127)	
Moderate AD				
Community	20,559	10,279–30,838	Gamma (15.37, 7.58)	
Nursing home	973	486–1459	Gamma (15.35, 0.016)	
Severe AD				
Community	20,724	10,362–31,086	Gamma (15.37, 7.52)	
Nursing home	1028	514–1542	Gamma (15.33, 0.0151)	
Drug (donepezil)	2884	1442–4325	Gamma (15.35, 0.0054)	AWP, [57]
Office visit due to treatment (per time)	83	42–125	Gamma (14.88, 0.1837)	[49]
CSF biomarker testing (per person)	324	162–487	Gamma (15.50, 0.0492)	[25]

AD Alzheimer’s disease, AE adverse event, AWP average wholesale price, CI confidence interval, CSF cerebrospinal fluid, MCI mild cognitive impairment, RR relative risk

^a CSF biomarker scores were calculated by the equation: $(-0.006) \times A\beta_{1-42} + 0.012 \times P\text{-tau}_{181p}$ [19]. The three risk groups were defined by the quintiles of the scores: high risk (the 3rd, 4th, and 5th quintiles), intermediate risk (the 2nd quintile), and low risk (the 1st quintile). Annual transition probability of each risk group was converted from the 6-year cumulative probability estimated by the Kaplan–Meier survival functions

^b Applied only to patients with severe AD and half of this to patients with moderate AD. We assumed MCI patients and patients with mild AD have the similar background all-cause mortality rate in terms of age

^c Annual probability derived from 6-month data by the exponential function $(0.18 = 1 - \exp[-0.0964 \times 2])$

^d Incorporated as disutility due to the treatment or lumbar puncture

hazard model for the best combination of CSF biomarker. The three risk groups were defined by the quintiles of the multi-biomarker score: high risk (the 3rd, 4th, and 5th quintiles), intermediate risk (the 2nd quintile), and low risk (the 1st quintile). We calculated the cumulative probability of progression to AD for each risk group using the Kaplan–Meier survival functions. For each risk group, we converted the 6-year cumulative probability into an annual probability of progression to AD (conditional on still being in the MCI state) and used this annual probability in our decision model, assuming a constant probability over the 6 years.

For transitions among AD stages, we used probabilities estimated by Spackman et al., who analyzed data from the Uniform Data Set of the National Alzheimer Coordinating Center [40]. They reported estimated probabilities of stage-to-stage transitions and probabilities of community-to-nursing-home transitions conditional on AD stage. Based on the rule of conditional probability, we calculated the

combined stage and nursing home transition probabilities (e.g., moving from mild AD community setting to mild AD nursing home) by multiplying these two transition probabilities together. We assumed that the risk of transitioning from community to nursing home conditional on AD stage is as reported and does not change for those persons who progress to different AD stages within the year.

2.3.2 Treatment Effectiveness

A recent Cochrane review [36] reported the relative risk (RR) of progression to dementia as 0.84 (95% CI 0.70–1.02) over 3 years (although effects for year 1 and year 3 were borderline significant) in MCI patients treated with a ChEI. Namely, it represents a 16% reduction of the annual progression risk from MCI to AD. In our base-case analysis we assumed that the effect persisted for only the first 3 years of treatment based on the synthesized results of the review.

The effectiveness parameter of ChEI treatment applied to patients with moderate AD was derived directly from an RCT [42], but we computed the RR for patients with mild AD using the data provided in the same RCT due to lack of directly applicable information. The RRs were 0.58 (95% CI 0.35–0.76) and 0.95 (95% CI 0.64–1.41) for patients with mild AD and moderate AD, respectively. In other words, mild AD patients treated with ChEIs experience a 42% reduction in the annual risk of transitioning to either moderate or severe AD, whereas the reduction was 5% for moderate AD patients receiving treatment transitioning to severe AD.

2.3.3 Adverse Events (AEs) Associated with Treatment

We used the result from a systematic review [43] for the annual risk of AEs (0.23) in the placebo arm of donepezil trials for MCI patients as the baseline risk for both MCI and AD patients receiving no treatment in our model. The reported RR of overall AEs between the treatment and the control groups for MCI patients was 1.09 (95% CI 1.02–1.16) [36]. For AD patients, we converted the reported odds ratio (OR) [44] to RR using methods from the Cochrane Handbook [45]. The converted RR was 2.09 (95% CI 1.81–2.40).

Despite a low frequency of complications for lumbar puncture [46], such as post-lumbar puncture headache, especially in the elderly population [47, 48], we took into account AEs due to CSF biomarker testing in the present study.

2.3.4 Withdrawal of Cholinesterase Inhibitor (ChEI) Treatment

We assumed that if patients discontinued treatment, they would experience the same risks of transitioning to the next health state as untreated patients. We did not assume any residual effects of treatment. In addition, MCI patients who discontinued the treatment would not be subsequently treated, even though they converted to AD. A systematic review [44] of 10 RCTs examining the efficacy of ChEIs among AD patients showed that more patients discontinued therapy due to AEs in the treatment group (18%) than in the placebo group (8%) within a study period of 6 months for all but two studies. We derived an annual withdrawal probability of 18% (95% CI 13–22%) conditional on experiencing an AE. Due to data availability, we applied this annual probability derived from AD patients to MCI patients as MCI is considered as the prodromal stage of AD [5] and the medication considered in the present study is one of the ChEIs. We also calculated the annual probability of withdrawal from treatment due to other reasons (excluding AEs) as 4.6% (95% CI 3.5–5.8%) and 11% (95%

CI 10–12%) for MCI and AD patients receiving treatment, respectively.

2.3.5 Health Utilities

We assigned health-related quality-of-life weights to disease severity and residential settings based on analyses by Neumann et al. [49, 50], because it was one of the few studies that estimated health utilities for joint states defined by disease severity and residential settings. In the study, they acquired quality-of-life weights, stratified by disease stage and setting, using the Health Utilities Index Mark II (HUI:2), which was administered in a companion, cross-sectional study of 528 caregivers of AD patients in the US [50]. Caregivers were asked to answer the questionnaire as the proxy respondents. Later, the responses to the questionnaire were converted into preference weights using the HUI:2 multi-attribute utility function [51]. Due to the absence of a range of quality-of-life weights by residential settings reported in their study, we applied the estimates of the standard error for AD patients dwelling in the community to AD patients in the nursing home. In addition, we also accounted for the quality-of-life decrement resulting from AEs due to the treatment, which was specified at 0.05 [29] as long as the treatment was provided. This disutility was accounted for by multiplying the assigned utility for each relevant state (e.g., MCI, mild AD, or moderate AD) by 0.95. The one-time disutility of 0.01 following the lumbar puncture (for CSF biomarker testing) was derived from the literature where the assumption was made [52].

2.3.6 Excess Mortality

The annual excess mortality rate among patients with severe AD was estimated at 0.11 by the additive model [53, 54]. We assumed that patients with moderate AD would experience half of the excess rate (i.e., we added 0.055 to the background death rates for patients in the moderate AD stage) and tested this assumption with a multiplier (range 10–90%) of excess mortality in the sensitivity analysis. We assumed that this additive effect is the same regardless of the patients' age or gender [53]. We assumed that the mortality rate for patients in the MCI and mild AD stage is equal to the background all-cause mortality rate.

2.3.7 Costs

We took a modified US societal perspective to include medical costs, and time costs of informal caregiving in the CEAs. In addition, the healthcare sector perspective (informal costs excluded) was also considered.

Formal and informal care We used the cost estimates reported by Leon et al. [55] for patients with AD based on severity and residential (community or nursing home) setting. These costs include both formal (paid health services) and informal care (defined as paid and unpaid services) for AD patients, where informal costs were estimated by replacement wages. We converted monthly costs to annual costs to assign to the relevant health states in our model. Because the variance (95% CI) of costs was not reported in the study, we assumed that the cost estimate for each health state in the model was 50% lower or higher from the mean of point estimates for the lower bound and the upper bound, respectively.

For the costs incurred in the MCI stage, we used data from Leibson et al. [56] to inform formal healthcare costs, including medical costs, pharmaceuticals, and informal healthcare costs (home care, assisted living, and transport) for MCI patients.

We did not account for the non-healthcare direct costs resulting from the loss of productivity of patients due to disease progression because we targeted the 65-year-old population. The CEA results presented included both formal and informal costs unless specified.

Medication We based the unit costs for AD medications on the average wholesale price reported in the Red Book [57]. The daily costs for these drugs were calculated based on their recommended dose and usage from the licensed labels. Because the drug is currently off-patent, we derived the medication cost at the available market price (US\$7.79) per day (the cost for donepezil 5 mg is the same as 10 mg) and the largest pack size. We estimated the annual drug costs as $365.25 \times \text{US\$}7.79 = \text{US\$}2845$. For the follow-up cost due to the treatment, we continued the assumption made by a previous study [49] that donepezil would induce two and one extra office visits every year along with the treatment effect duration for MCI and AD patients, respectively. One office visit was associated with US\$82 as estimated by the previous study [49].

CSF biomarker testing The cost of CSF biomarker analysis, a one-time cost per patient, was estimated using the cost data from Centers for Medicare and Medicaid Services hospital outpatient fee schedule [25].

Because the ChEI treatment-induced AEs are generally mild or moderate [36, 58], we did not consider the costs of treating AEs but the disutility associated with those AEs. All cost estimates were inflated to 2016 US dollars using the Consumer Price Index [59] if needed.

2.4 Analyses

2.4.1 Base-Case Analysis

We calculated expected discounted lifetime costs and discounted QALYs, generated from the probabilistic

sensitivity analysis (PSA) to account for the nonlinear feature of Markov models [60, 61], for each of the six strategies with the best estimates for all of the input parameters and preferred set of assumptions. Results were presented as incremental cost-effectiveness ratios (ICERs), measured as the additional cost per additional QALY gained. The most effective strategy with an ICER that is below the designated willingness-to-pay (WTP) threshold (i.e., the ratio of US\$100,000 per QALY suggested by Neumann et al. [62] in the US setting) would be declared as a cost-effective strategy. After the cost-effective strategy was decided, we further calculated its ICER in the 2.5th and 97.5th percentiles using the same PSA results mentioned above.

2.4.2 Sensitivity Analysis

We conducted deterministic sensitivity analyses and PSA to evaluate uncertainty with respect to all the parameters included in the simulation models. Table 1 presents the parameter values and their corresponding distributions. To ensure only meaningful scenarios, we required that the rank order of QALY weights in each PSA iteration was aligned with disease severity and residential settings [63], which implied that the health utility of $u(\text{MCI}) > u(\text{mild AD}) > u(\text{moderate AD}) > u(\text{severe AD})$ and $u(\text{community}) > u(\text{nursing home})$, applying the preference-ordering algorithm developed by Goldhaber-Fiebert and Jalal [64]. We presented PSA results using the cost-effectiveness acceptability curve (CEAC) [65], and further plotted the cost-effectiveness acceptability frontier (CEAF) [66, 67] on the top of CEAC to simultaneously present the optimal strategy and the level of uncertainty associated with that strategy at different WTP thresholds.

2.4.3 Scenario Analysis

We conducted the scenario analysis, assuming patients are allowed to receive treatment in the AD stage even if they were treated in the MCI stage, because this is the standard of care, even though the effectiveness of MCI treatment is unclear. Because it is not known whether treatment effectiveness for AD is the same for treated and untreated MCI patients, we further examined diminished treatment effectiveness in the AD stage for treated MCI patients. For untreated MCI patients, the treatment effectiveness in the AD stage was held constant at the base-case value (RR 0.58).

All analyses were performed in TreeAge Pro 2016 (TreeAge Software, INC, Williamstown, MA, USA), and Microsoft Excel (Microsoft Corp., Redmond, WA, USA).

3 Results

3.1 Base-Case Analysis

Table 2 shows discounted costs and discounted QALYs for each strategy (the disaggregated total costs and QALYs by health states for each strategy is presented in Appendix A and B, respectively). In addition, we summarized the costs of medication, office visits, and CSF biomarker testing separated from total costs by disease stages and settings in Appendix C, see electronic supplementary material [ESM]). The most effective and most costly strategy was to test and treat MCI patients at low risk, which resulted in an ICER of US\$37,700 per QALY compared with not testing and not treating any MCI patient. The ICERs for this strategy at the 2.5th and 97.5th percentiles were US\$18,900 and US\$50,100 per QALY, respectively. In addition, results indicated that testing and treating patients at low risk was still the most cost-effective strategy with an ICER of US\$59,800 per QALY from a healthcare sector perspective (see Appendix D and E for disaggregated costs results in the ESM).

3.2 Deterministic Sensitivity Analysis

Table 3 summarizes the selected one-way sensitivity analysis results with ICERs and corresponding comparators for the key parameters (see Appendix F in the ESM for results with the remaining parameters). Our base-case results were most sensitive to variations in the effectiveness of treatment. For example, if the treatment effectiveness for mild AD patients was better than our base-case estimate, or the treatment effectiveness for MCI patients was worse than our base-case estimate, then no testing and no MCI treatment would be cost-effective. Our results were also sensitive to the health utility assigned to patients in the MCI stage. The cost of medication (donepezil) had little impact on our base-case results.

Table 2 Base-case results (per patient) of performing CSF biomarker testing and subsequently treating MCI patients based on their risk levels of progression to AD

Strategy	Cost (US\$)	QALYs	ICER (US\$/QALY) ^a
Test and treat high or intermediate risk	270,593	7.471	
Test and treat high risk	270,735	7.475	Weakly dominated
No testing and treat all MCI patients	271,083	7.509	12,800
No testing and no MCI treatment	275,302	7.627	Weakly dominated
Test and treat low or intermediate risk	276,286	7.647	Weakly dominated
Test and treat low risk	276,428	7.651	37,700

If patients received treatment in the MCI stage, no treatment would be provided when they convert to AD AD Alzheimer's disease, CSF cerebrospinal fluid, ICER incremental cost-effectiveness ratio, MCI mild cognitive impairment, QALYs quality-adjusted life-years

^a The value was rounded to the nearest \$100. A weakly dominated strategy is a strategy with a higher ICER than a more costly strategy

3.3 Probabilistic Sensitivity Analysis

Figure 2 shows the CEAC and the CEAF generated from our PSA. With the maximized expected outcomes shown in the base-case analysis, the strategy of testing and treating MCI patients at low risk showed a 26% probability of being cost-effective at a WTP of US\$100,000 per QALY, whereas it was 30% for no testing and no MCI treatment. Testing and treating MCI patients at low risk was the strategy with the highest probability of being cost effective (29%) for a WTP of US\$150,000 per QALY. Strategies of testing and treating high risk, and testing and treating high or intermediate risk showed a lower likelihood of cost-effectiveness compared with other test-and-treat strategies. They were less likely to be cost-effective when WTP was higher than US\$30,000 per QALY.

3.4 Scenario Analysis

As expected, QALYs increased with the increasing number of treated MCI patients and the strategy of no testing and treating all MCI patients was associated with the highest cost and highest QALYs, with an ICER of US\$27,600 per QALY, given the relaxed assumption that patients are allowed to receive treatment in the AD stage even if they were treated in the MCI stage. All of the testing strategies were either strongly or weakly dominated. In addition, results of examining the diminished AD treatment effectiveness for treated MCI patients and a constant AD effectiveness for untreated MCI patients indicated that the strategy of no testing and treating all MCI patients remained the best strategy when the RR of the treatment effectiveness for AD was not worse than 0.65 at a WTP threshold of US\$100,000 per QALY (not shown).

4 Discussion

In this study, we sought to evaluate the potential value of using CSF biomarkers to target treatments, based on the best available data, for a subset of MCI patients according

Table 3 Incremental cost-effectiveness ratios of one-way sensitivity analysis results with key parameters

Analysis ^a	Test-and-treat strategy					
	Test and treat low risk	Test and treat low or intermediate risk	No test and no MCI treatment	No test and treat all MCI	Test and treat high risk	Test and treat high or intermediate risk
Base-case	37,700 ^b	Weakly DOM	Weakly DOM	12,800 ^c	Weakly DOM	–
Annual probability of progression from MCI to AD						
At low risk, 1%	38,500 ^b	Weakly DOM	Weakly DOM	19,000 ^c	Weakly DOM	–
At low risk, 16%	Weakly DOM	Weakly DOM	35,600 ^b	–	Weakly DOM	Weakly DOM
At intermediate risk, 3%	Weakly DOM	40,700 ^b	Weakly DOM	20,400 ^c	–	Weakly DOM
At intermediate risk, 22%	38,100 ^b	Weakly DOM	Weakly DOM	9400 ^c	Weakly DOM	–
At high risk, 17%	64,400 ^d	Weakly DOM	36,200 ^b	9500 ^c	Strongly DOM	–
At high risk, 33%	64,400 ^d	Weakly DOM	38,000 ^b	9500 ^c	Strongly DOM	–
Treatment effectiveness (RR)						
Mild AD, 0.35	Strongly DOM	Strongly DOM	16,400 ^e	Strongly DOM	7500 ^c	–
Mild AD, 0.76	Strongly DOM	438,000 ^b	Strongly DOM	5800 ^c	Strongly DOM	–
Moderate AD, 0.64	199,000 ^d	Strongly DOM	27,800 ^b	8800 ^c	Weakly DOM	–
Moderate AD, 1.41	64,400 ^d	Weakly DOM	37,300 ^b	9500 ^c	Strongly DOM	–
MCI patients, 0.70	Strongly DOM	131,800 ^b	Strongly DOM	–	Strongly DOM	Strongly DOM
MCI patients, 1.02	Strongly DOM	Strongly DOM	10,300 ^e	Strongly DOM	–	Strongly DOM
Treatment harm						
Annual prob. of AE (control), 20%	75,300 ^d	Strongly DOM	34,400 ^b	9300 ^c	Strongly DOM	–
Annual prob. of AE (control), 26%	65,200 ^d	Weakly DOM	36,600 ^b	9600 ^c	Strongly DOM	–
AEs in MCI (RR), 1.02	69,600 ^d	Weakly DOM	37,500 ^b	8600 ^c	Strongly DOM	–
AEs in MCI (RR), 1.16	64,700 ^d	Weakly DOM	33,300 ^b	10,200 ^c	Strongly DOM	–
AEs in AD (RR), 1.81	79,200 ^d	Strongly DOM	33,400 ^b	9400 ^c	Strongly DOM	–
AEs in AD (RR), 2.40	Strongly DOM	Strongly DOM	10,200 ^b	Strongly DOM	–	Strongly DOM
Withdrawal due to AE, 13%	78,700 ^d	Strongly DOM	44,500 ^b	7500 ^c	Strongly DOM	–
Withdrawal due to AE, 22%	64,800 ^d	Weakly DOM	35,600 ^b	10,700 ^c	Weakly DOM	–
Health utility						
MCI patients, 0.58	995,200 ^d	Strongly DOM	26,500 ^e	Weakly DOM	15,400 ^c	–
MCI patients, 0.88	Strongly DOM	52,800 ^b	Weakly DOM	6200 ^c	Strongly DOM	–
Health utility						
AE, 0.916	53,500 ^f	53,000 ^d	44,900 ^b	8600 ^c	Strongly DOM	–
AE, 0.976	84,900 ^d	Strongly DOM	31,700 ^b	10,300 ^c	Strongly DOM	–
Lumbar puncture, 0.009	78,600 ^d	Strongly DOM	35,500 ^b	9000 ^c	Strongly DOM	–
Lumbar puncture, 0.012	61,300 ^d	Weakly DOM	37,300 ^b	9700 ^c	Strongly DOM	–
Annual costs						
MCI, US\$3733	72,100 ^d	Strongly DOM	35,500 ^b	8600 ^c	Strongly DOM	–
MCI, US\$11,200	67,800 ^d	Weakly DOM	35,500 ^b	10,200 ^c	Strongly DOM	–
Formal costs for patients dwelling in the community						
Mild AD, US\$4690	96,600 ^d	Strongly DOM	14,300 ^e	Weakly DOM	–	Strongly DOM
Mild AD, US\$14,070	95,400 ^f	60,400 ^b	Strongly DOM	–	Strongly DOM	Strongly DOM
Moderate AD, US\$6929	59,100 ^d	Weakly DOM	42,100 ^b	4400 ^c	Strongly DOM	–
Moderate AD, US\$20,788	80,400 ^d	Weakly DOM	28,900 ^b	14,500 ^c	Weakly DOM	–

Table 3 continued

Analysis ^a	Test-and-treat strategy					
	Test and treat low risk	Test and treat low or intermediate risk	No test and no MCI treatment	No test and treat all MCI	Test and treat high risk	Test and treat high or intermediate risk
Severe AD, US\$10,445	53,900 ^f	47,000 ^b	Weakly DOM	1300 ^c	Strongly DOM	–
Severe AD, US\$31,334	78,600 ^d	Weakly DOM	36,100 ^b	21,500 ^c	7400 ^c	–
Formal costs for patients dwelling in a nursing home						
Mild AD, US\$25,432	75,900 ^d	Weakly DOM	26,800 ^b	17,600 ^c	10,700 ^c	–
Mild AD, US\$76,297	57,000 ^d	Weakly DOM	45,300 ^b	3400 ^c	Strongly DOM	–
Moderate AD, US\$27,681	62,800 ^d	Weakly DOM	38,200 ^b	8700 ^c	Strongly DOM	–
Moderate AD, US\$83,043	70,800 ^d	Weakly DOM	35,200 ^b	9900 ^c	Strongly DOM	–
Severe AD, US\$29,664	62,500 ^f	49,700 ^b	Weakly DOM	1600 ^c	Strongly DOM	–
Severe AD, US\$88,991	88,700 ^d	Weakly DOM	22,700 ^c	Weakly DOM	2400 ^c	–
Excess mortality in moderate AD						
Multiplier, 10%	74,700 ^d	Weakly DOM	26,200 ^b	20,800 ^c	6200 ^c	–
Multiplier, 90%	57,800 ^d	Strongly DOM	44,600 ^b	2200 ^c	Strongly DOM	–

The comparator strategy for the calculation of ICERs was varied by the value of parameters tested

AD Alzheimer's disease, AE adverse event, DOM dominated, ICERs incremental cost-effectiveness ratios, MCI mild cognitive impairment, RR relative risk

^a The value was rounded to the nearest \$100. – indicated the reference strategy. A weakly dominated strategy is a strategy with a higher ICER than a more costly strategy, and a strongly dominated strategy is a strategy that is more costly but less effective

^b Compared with no testing and treat all MCI patients

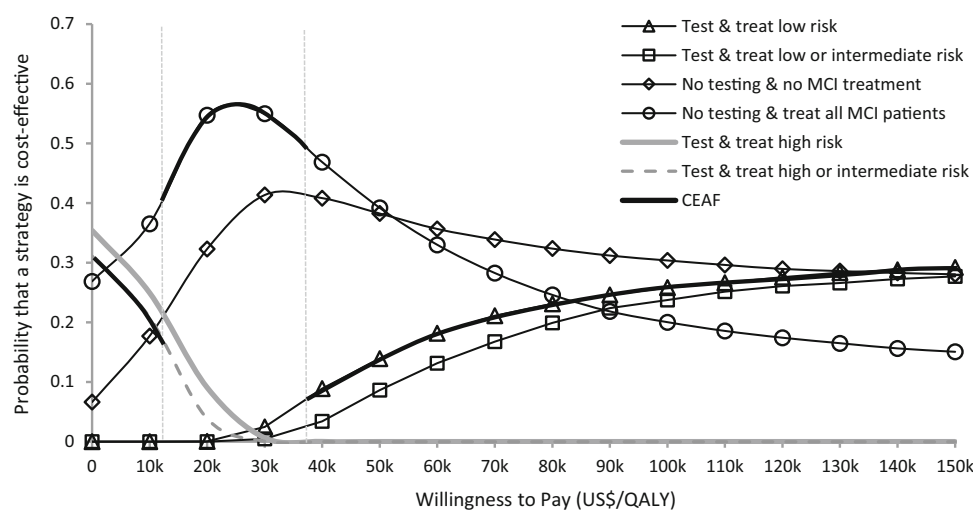
^c Compared with test and treat high or intermediate risk

^d Compared with no testing and no MCI treatment

^e Compared with test and treat high risk

^f Compared with test and treat low or intermediate risk

Fig. 2 Cost-effectiveness acceptability curve showing the probability that a strategy is cost-effective at various willingness-to-pay thresholds. Vertical lines represent the incremental cost-effectiveness ratio for strategies of 'no testing and treat all MCI patients' (US\$12,800/QALY), and 'test and treat low risk' (US\$37,700/QALY). CEAF cost-effectiveness acceptability frontier, MCI mild cognitive impairment, QALYs quality-adjusted life years



to their risk level of progression to AD. Our results indicated that testing and treating patients at low risk was cost-effective with an ICER of US\$37,700 per QALY, which was more beneficial than treating patients at high risk, although such a practice would be contradictory to the

widely held belief that interventions should usually be aimed at high-risk patients. However, the low-risk patients in our case were not comparable to the low-risk patients in the general population. They were instead low-risk patients among the MCI population—that is, referred to specialty

clinics—and thus have a higher risk of progression to AD than the general population. Thus, the conventional rationale (targeting high-risk patients) might not be applicable in our case. Moreover, this finding may be associated with our assumption that treated MCI patients were ineligible for treatment if they converted to AD, and that MCI patients at higher risk faced a relative short time until clinical diagnosis of AD in our model [68, 69]. As a result, the trade-off between treatment effectiveness for MCI patients and for patients with mild AD was a key driver of this finding. With the more conservative assumption of treatment effectiveness for MCI patients utilized here when compared with other published models using a hypothetical DMT(RR 0.5) [29, 30, 70, 71], our finding may provide a more realistic picture of potential treatment effectiveness for MCI and AD patients.

Another possible explanation for the study finding is that treatment duration for MCI patients at high risk may be truncated (as we assumed the maximum treatment period was 3 years based on the available evidence) due to the conversion to AD. However, with results showing that time in MCI stage (without intervention) was 3.16, 6.48, and 8.67 years for patients at high, intermediate, or low risk, respectively, and a constant probability of transitioning from MCI to AD for high-risk patients was 0.244 annually, the treatment duration was less likely to be truncated at Year 3 for this group. It is also possible that the treatment response varied by MCI patients' CSF biomarker profiles (i.e., patients at high risk had a better response to the ChEI therapy than patients at intermediate or low risk). By assuming that MCI patients at high, intermediate, and low risk had 100%, 80%, and 60% response to ChEI treatment, respectively, results of additional analyses indicated that no testing and no MCI treatment was cost-effective with an ICER of US\$30,000 per QALY, while it was US\$106,300 per QALY for treating patients at low risk (results not shown).

As indicated in the study by Sköldunger et al. [31], patients will live longer as a consequence of the treatment, and in turn accrue higher costs if providing treatment in the AD stage but not in the MCI stage. In our case, the strategy of 'no testing and no MCI treatment' reflected highest costs in the mild AD stage (due to the treatment costs and longer period in the mild AD stage, Appendix G, see ESM) but lowest costs in the moderate and severe AD stage. This may be explained by (1) a great difference between the treatment effectiveness for mild AD (RR 0.58) and moderate AD (RR 0.95), which implies that there is almost no treatment effect for moderate AD; (2) the time difference in the states (Appendix G, see ESM); and (3) age- and disease severity-related mortality rates. In this strategy, simulated patients were older when they progressed to moderate AD (6.285 QALYs in the MCI and mild AD

stage), and thus with higher mortality rates, compared with the relatively younger population (6.023 QALYs in the MCI and mild AD stage) in the strategy of 'no testing and treat all MCI patients'. Moreover, due to the modest treatment effectiveness for moderate AD, simulated patients with moderate AD either progressed to severe AD or death quickly. In addition, our findings are in line with the Sköldunger et al. study [31] oppositely with more time in the MCI stage and less time in the AD stage as a whole (the condensing effect) when treating MCI but not AD (no testing and treat all MCI patients).

It is of value to investigate the feasibility of the treatment continuum from MCI to AD stages. Not surprisingly, the scenario analysis where treatment was allowed in both MCI and AD stages produced greater benefits than when treatment was only allowed in one or the other. This implied that alternative interventions that allowed for the effectiveness to be carried over from MCI to AD stages would be considered as an optimal strategy. Furthermore, sensitivity analyses with a diminished AD treatment effectiveness for treated MCI patients and a constant effectiveness for untreated MCI patients indicated that no testing and treating of all MCI patients was cost-effective if the AD effectiveness for treated MCI patients was not worse than RR 0.65.

Although previous studies concluded that CSF biomarker testing could allow one to identify MCI patients who are best suited for potential pharmacological treatment [19], this study suggests that treating low-risk MCI patients might lead to a greater benefit by slowing the progression to AD. That is to say, clinicians or policy makers might consider the potential to intervene not only on higher-risk patients but on low-risk MCI patients when they initiate the disease management plan. Moreover, with the plausibility that MCI patients at high risk may be close to the threshold of AD diagnosis and that MCI patients in general are at a higher risk for progression than the general population, the findings again suggest that the MCI population might benefit greatly from early intervention with the use of CSF biomarker testing from a cost-effectiveness perspective. Further studies are needed to re-evaluate the benefits of early detection or diagnosis when the DMT is available.

It is possible that the most cost-effective (optimal) strategy may not have the highest probability of being cost-effective [67]. In our case, the strategy of testing and treating patients at low risk was most cost-effective in the base-case analysis; however, its probability of being cost-effective in the PSA was only 26% at a WTP of US\$100,000 per QALY. The results showed that there is a high degree of decision uncertainty surrounding the optimal strategy in the present study even with the best available evidence. In this case, the decision of whether to treat MCI patients or not may benefit from conducting

value of information analysis to assess the potential gains to further research [72] such as gathering more information on the key parameters (i.e., the treatment effectiveness for MCI), before making a decision. However, there is a trade-off between the potential gain for more research and the concurrent consequences (loss of potential benefits from early interventions) of not taking any action.

Our study has several limitations. Our modeling results were heavily subject to the inconclusive findings of treatment effectiveness. The treatment effectiveness of ChEIs for MCI patients was derived from a recent Cochrane review study [36] where authors reported evidence of minor benefits (effects for year 1 and year 3 were borderline significant; effects for year 2 were significant) with limitations and uncertainty, and further concluded that ChEI treatment is not recommended for MCI patients due to weak evidence. Compared with other similar studies using a hypothetical treatment effectiveness (RR 0.5) [29–31, 70, 71, 73], however, our assumption was relatively conservative (RR 0.84) and was based on point estimates reported from the most recent review evidence. Moreover, by applying the empirical data, our approach should better reflect what the real potential treatment benefits might be, acknowledge the debate of whether we should treat MCI patients or not based on the current evidence, and reflect that if a decision must be made, it should be made based on the available evidence [38].

No recent meta-analyses of treatment effectiveness for AD patients were presented as the measure of the RR, which was built-in in our model to reflect the treatment-associated reduction on the risk of progression between the AD stages. Most studies [44, 74, 75] reported the effect size of this parameter as the point difference of cognitive tests, such as Mini-Mental State Examination (MMSE) or the AD and Associated Disorders Cognitive Scale between treatment and control arms instead of the risk reduction of transitions to more severe stages of AD (presented as the RR). Hence, we applied the information from point differences of MMSE scores along with the proportion of patients with mild AD and moderate AD in an RCT to indirectly derive the RR of progression from the mild to moderate AD stage for the treatment group versus the control group.

The cost information [55] applied in this study is outdated due to the unavailability or inapplicability of recent data. Changes in many social and cultural factors are very likely to influence the cost estimates. However, we found that our base-case findings were robust under wide ranges of cost estimates examined in sensitivity analyses.

We were not able to account for the possible double treatment effects, which may lead to a potential bias of the study findings, resulting from the treatment effect embedded in the estimated transition probabilities derived

from the scholarly literature where about 70% of their analysis sample were reported using AD medication. However, the cost-effectiveness metrics (ICERs) were the relative difference between the different test-and-treat strategies in terms of accrued costs and QALYs. In this case, the treatment effects should be compensated or minimal, which should not have major impact on our findings.

We acknowledge several limitations, such as solely using cognition as a driver of disease progression or a limited number of health states to present the natural history of disease due to the use of Markov modeling techniques [76, 77] existing in the current simulation models in AD. However, to build a model including indicators other than cognitive function would increase the complexity of the model structure, the trade-off between the complexity and transparency of a simulation model should be well balanced. The merit of using Markov models is that they provide a relatively transparent analysis and accessibility when compared with other models, such as discrete-event simulation models, which may induce overspecification where models may become more complex than necessary (as a result of computational challenges) to elicit accurate results [78].

We included a subset of all possible test-and-treat strategies in the CEA. Our rationale is that we attempted to find a threshold of CSF biomarker levels (a positive and ordinal association with risk levels of AD) that would decide which subset of MCI patients to treat from a cost-effectiveness perspective. Therefore, it would not be logical to include strategies of ‘treat MCI patients at intermediate risk only’ or ‘treat MCI patients at low or high risk’ in the CEA due to the ordinal nature of the risk levels. Moreover, results of additional analyses including these two strategies indicated that they were both weakly dominated strategies.

For the transitions in the residential settings, we assumed once AD patients enter a nursing home they would remain in the institution until death. This may not reflect the current practice that patients transition among hospitals, home, and long-term care facilities within a short period of time. However, in our case, most of the patients who entered the nursing facility had severe AD. Accordingly, given the similar disease severity, the accumulative healthcare costs of staying in the nursing facility should be similar to the transitions among hospitals, home or long-term care facilities within the same periods of time from a social perspective.

We acknowledge that using CSF biomarkers only to categorize MCI patients into different risk levels of progression to AD may omit the potential added values from including other risk factors, such as patient demographics and their clinical characteristics.

5 Conclusion

Based on the best available evidence regarding treatment effectiveness for MCI, this study suggests that performing CSF biomarker testing for early targeted treatments among MCI patients may be cost-effective. Interpretation of these results should be made with caution. Further research is needed to reduce the high degree of uncertainty regarding testing and treating MCI patients.

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Compliance with Ethical Standards

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Conflict of interest TLM reports no conflicts of interest. RLK reports no conflicts of interest. JRM reports no conflicts of interest. JEG reports no conflicts of interest. JAN reports no conflicts of interest. KMK reports no conflicts of interest.

Data availability statement All data generated or analyzed during this study are included in this published article (and its electronic supplementary material files).

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