

Modeling the Early Identification and Intervention of
Alzheimer's Disease

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Abstract

Advances in neuroimaging and biomarkers now provide the ability to detect evidence for the pathophysiological process of Alzheimer's disease (AD) before clinically detectable dementia. Because of these findings, AD research has begun to focus on the preclinical or prodromal stages of the disease. For example, many clinical trials and laboratory-based studies have examined the clinical benefit of earlier AD intervention, such as pre-symptomatic stages of AD, based on the belief that it is more likely to achieve disease modification. The economic evaluation of potential interventions on AD, which mainly extends to include the earlier disease stages by using biomarker testing to predict the risk of disease progression, needs to be updated. Accordingly, the overall objective of this thesis is to quantify the value of using cerebrospinal fluid (CSF) biomarker testing for early-targeted treatment on patients with mild cognitive impairment who are at risk of developing AD. Firstly, I examined whether CSF biomarker testing can categorize MCI patients into different risk groups of developing AD, and thus allowing for targeted early treatment on MCI patients. Secondly, I conducted a cost-effectiveness analysis to evaluate the different treatment strategies with or without testing information involved by developing a decision model to synthesize all relevant evidence and project the expected value of outcomes of interest for each proposed alternative. Finally, I further address key challenges based on the current evidence by estimating the societal value of reducing uncertainty surrounding the decision model through further research. Economic evidence about the relative costs and outcomes of health and social care can assist decision makers in determining the best use of scarce healthcare resources.

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List of Abbreviations

AD	Alzheimer's disease
aMCI	Amnesic MCI
A β	β -amyloid
ADAS 13	Alzheimer's Disease Assessment Scale
ADNI	Alzheimer's Disease Neuroimaging Initiative
APOE ϵ 4	Apolipoprotein ϵ 4
AUC	Area under the ROC curve
AE	Adverse events
CSF	Cerebrospinal fluid
CDR-SB	Clinical dementia rating sum of boxes
Cox PH model	Cox proportional hazards model
CIND	Cognitive impairment without dementia
ChEIs	Cholinesterase inhibitors
CEA	Cost-effectiveness analysis
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CI	Confidence interval
CPI	Consumer price index
CEAC	Cost-effectiveness acceptability curve
DSA	Deterministic sensitivity analysis
EVPI	Expected value of perfect information
EVSI	Expected value of sample information
ENBS	Expected net benefit of sample
FDA	Food and Drug Administration
GAM	Generalized additive model
ICD	International Classification of Diseases
IWG	International Working Group
IATI	Innotest amyloid-tau index
ICERs	Incremental cost-effectiveness ratios
INHB	Incremental net health benefit
MRI	Magnetic resonance imaging
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Exam
naMCI	Non-amnesic MCI
MCMC	Markov chain Monte Carlo
NIA-AA	National Institute on Aging-Alzheimer's Association
NACC-UDS	National Alzheimer Coordinating Center- the Uniform Data Set
NHB	Net health benefit
NMB	Net monetary benefit
PET	Positron emission tomography
P-tau _{181p}	Phosphorylated tau
PSA	Probabilistic sensitivity analysis
QALYs	Quality-adjusted life years
ROC	Receiver operator characteristic
RR	Relative risk
SD	Standard deviation
T-tau	Total tau
VOI	Value of information
WTP	Willingness to pay

Chapter 1. Background

1.1 Alzheimer's disease

1.1.1 Definition and diagnosis

Alzheimer's disease (AD), the most common type of dementia, is a devastating neurodegenerative disease that impairs memory, thought, and behavior; reduces quality of life; and decreases survival. It is the most common cause of dementia, accounting for 60 to 80 percent of all dementia cases.¹ No single test can prove a person has AD. A clinical diagnosis is made through several assessments, including a medical history, a mental status evaluation, a physical and neurological examination and laboratory tests, that consider all possible causes.² Dementia is incorporated into the diagnostic categories of major and mild neurocognitive disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) in 2013.³ For both major and mild neurocognitive disorders, DSM-5 instructs physicians to specify whether the condition is due to AD or other causes.¹ The criteria established by the National Institute of Neurological and Communicative Diseases and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for a diagnosis of probable AD (i.e., no other cause for the symptoms can be found) include: 1) dementia established by examination and objective testing; 2) deficits in two or more cognitive areas; 3) progressive worsening of memory and other cognitive functions; 4) no disturbance in consciousness; and 5) onset between ages 40 and 90. Recently, the NINCDS-ADRDA also defined three stages of AD - the preclinical, the prodromal and the dementia stages, which allows AD to be diagnosed before the onset of clinical symptoms, such as memory loss. In addition, they recommend the use of biomarker tests to assist in the diagnosis of the presence of disease.¹ However, more research is needed before this proposed operational research criteria and guidelines could be used in clinical settings.^{1,4}

1.1.2 Burden of disease

An estimated 5.2 million people in the US had AD dementia in 2014, and it is now the sixth leading cause of death.¹ As age is the biggest risk factor for the disease, with the aging of the population, the disease burden in the US will increase to an estimated 7.7 million cases in 2030 and 11 to 16 million cases in 2050.⁵ These numbers do not include the large number of people with mild cognitive impairment (MCI), a significant proportion of whom will progress to AD. Patients with AD are high users of health care and long-term care services. In the US, there are more than 15 million family caregivers who provide unpaid care for people with AD and other dementia are under great emotional burden.¹ AD and other types of dementia cost Medicare \$113 billion per year and Medicaid \$37 billion per year. The total annual direct costs of AD are estimated at \$214 billion.¹

AD places considerable and increasing burden on patients, caregivers and society, as more people live long enough to become at-risk. As their independence continues to decline, AD patients place an increasing physical, psychological, and financial burden on family caregivers. As a result, they are frequently placed in residential care/assisted living facilities, nursing homes, or geropsychiatric hospitals.

1.1.3 Phases of AD

Based on clinical experience and analysis of cognitive testing, the clinical disease stages of AD can be divided into three phases in a recent workshop.⁶ The first phase is a preclinical phase⁷ in which individuals are cognitively normal, but have some AD pathological changes.⁷ To some extent, labeling these individuals as having pre-symptomatic AD is hypothetical, because some of these individuals will die from other causes without ever expressing clinical symptoms.⁸⁻¹⁰ The assertion is that an asymptomatic individual with pathological changes that are indicative of AD has a higher

risk of becoming symptomatic if he or she lived long enough compared with those without any changes. The second phase is a prodromal phase of AD,⁴ commonly referred to as MCI,¹¹ and it is characterized by the onset of the earliest cognitive symptoms (typically deficits in episodic memory) that do not meet the criteria for dementia. The severity of cognitive impairment in the MCI phase of AD varies from the earliest appearance of memory dysfunction to more widespread dysfunction in other cognitive domains. This prodromal phase has recently taken on critical importance because of the potential it offers to treat and potentially delay the AD process at the point of its earliest manifestation. The final phase in the evolution of AD is dementia,¹² defined as impairments in multiple domains that are severe enough to produce loss of function. During this phase, the important clinical considerations are level of dementia severity and the rate of its progression. Pre-dementia phases of AD, including the preclinical and prodromal phases mentioned above, may serve as an opportunity for early detection with potential to delay the progression of AD. Many researchers in the field believe that future treatments to slow or stop the progression of AD will be most effective when administered during the preclinical and MCI stages of the disease.¹

1.1.4 Assessments of AD

AD is heterogeneous in its presentation and disease course across the main symptom domains of cognition, function, and behavior. Several instruments are commonly used to assess the severity of AD. The Clinical Dementia Rating scale (CDR)^{13,14} combines both cognitive and functional domains to determine the stage of AD patients. CDR is a five-point scale, which quantifies dementia severity from very mild (CDR-0.5) to mild (CDR-1), moderate (CDR-2), and severe (CDR-3) in addition to no cognitive impairment (CDR-0).¹⁵ The Mini-Mental State Examination (MMSE)¹⁶ is a 30-item screening tool for the assessment of cognitive impairment and also a common tool for determining the severity

of AD. The cut-offs used to define severity levels are not consistent across studies,¹⁷ but in general scores between 21 to 24 are considered mild, 10 to 20 moderate, and ≤ 9 points severe.¹⁸ The scale of AD and associated disorders (ADAS) was designed to measure the severity of the most important symptoms of AD.¹⁹ Its subscale ADAS-cog (total 70 points, with higher scores (≥ 18) indicating greater cognitive impairment) consists of 11 tasks measuring the disturbances of memory, language, praxis, attention and other cognitive abilities and is commonly used to estimate the treatment efficacy in the clinical trials. A four-point change on the ADAS-Cog at 6 months is considered as indicating a clinically important difference.^{20,21} The Global Deterioration Scale (GDS),²² which divided AD into 7 stage of ability, is based on implicit assumptions about the linearity, temporality, and interdependence of cognitive, functional, and behavioral impairment in the disease. The Allen Cognitive Levels (ACL) Assessment is an occupational therapy tool designed to characterize an individual's level of cognitive and adaptive functioning,^{23,24} which informs the level of assistance a person is likely to need in order to perform routine tasks (6 levels ranging from coma [0.8] to normal [6.0]), and how that person will perform in novel situations.

1.1.5 Currently available treatments for AD patients

The current standard of care for patients with mild to moderate AD includes treatment with cholinesterase inhibitors (ChEIs), including tacrine, donepezil, galantamine, or rivastigmine, to improve cognitive function,²⁵ and it can be started as soon as dementia is diagnosed.²⁶ Results of 10 randomized, double blind, placebo controlled trials (RCTs) demonstrated that treatment for 6 months with ChEIs at the recommended dose for people with dementia due to AD produced improvements in cognitive function, on average -2.7 points (95%CI: -3.0 to -2.3), in the midrange of the 70 point ADAS-Cog scale.²⁷ A few studies have also shown that ChEI treatment of AD patients reduces the

time required for family care, or delays the time until nursing home institutionalization becomes necessary.²⁸⁻³⁰ For example, in a 30-week RCT with an open-label extension, patients with mild to moderate AD who remained on tacrine and were receiving doses < 80 mg/d or < 120 mg/d were more likely to have entered a nursing home than patients on higher doses (odds ratios= 2.7 [95% CI: 1.4-5.2] or 2.8 [95% CI: 1.5-5.2], respectively).³¹ Wattmo et al.²⁹ found that a higher mean dose of ChEIs postponed institutionalization in AD patients (hazard ratio= 0.63, 95%CI: 0.47–0.85). Furthermore, Lopez et al.³⁰ showed in a comparison between treated and untreated matched AD cohorts that ChEI use was associated with a protective effect on nursing home admission (relative risk [RR]= 0.095, 95% CI: 0.03-0.30). On the other hand, in a 12-week RCT of donepezil treatment on patients with mild to moderate AD,³² results indicated the RR of entering institutional care in the donepezil group compared with placebo was 0.97 but not statistically significant (95% CI: 0.72-1.30). This is similar to what Gaugler et al. found in a systematic review, which concluded that studies of ChEI treatment in AD patients, with nursing home placement as an outcome measure, were inconclusive.³³ In general, The N-methyl-d-aspartate (NMDA) antagonist memantine has also been shown to improve cognitive function (language, memory, and praxis) in patients with moderate to severe AD (MMSE < 20) compared to placebo-treated patients in a post-hoc analysis.³⁴ In addition, the common non-cognitive neuropsychiatric symptoms of AD (such as mood disorder, agitation and psychosis) are often treated with prescribed medication, even though no existing drug is specifically indicated for their management.³⁵ To date, there is no treatment with a proven disease-modifying effect on underlying disease pathology of AD. While current guidelines support the use of ChEIs in patients with mild to moderate AD,³⁶ results from more recent clinical trials^{37,38} speculates that ChEI treatment may also be effective across all stages of AD, as well as for MCI.³⁹

1.2 Mild cognitive impairment

1.2.1 Definition of diagnosis

MCI is a condition in which a person has problems with memory, language or another essential cognitive function that are noticeable to others and show up on cognitive tests, but are not severe enough to interfere with daily life.⁴⁰ The diagnosis for amnesic MCI (aMCI) is usually established using the Petersen criteria,⁴¹ revised Petersen criteria (aMCI, **Table 1.1**),^{42,43} CDR equal to 0.5,^{13,15} or an MMSE score between 24 and 30.⁴⁴ The differentiation of dementia from MCI in general rests on the determination of whether or not there is significant interference in the ability to function at work or in usual daily activities.¹²

Table 1.1 Petersen's criteria for amnesic mild cognitive impairment.^{11,42}

Memory complaint usually corroborated by an informant
Objective memory impairment for age
Essentially preserved general cognitive function
Largely intact functional activities
Not demented

1.2.2 Subtypes of MCI

The term MCI was first used to refer to an early stage of AD dementia (i.e., aMCI). It was in widespread use after the introduction of the Petersen criteria⁴³ for aMCI, which subsequently became a subtype of a broader concept of MCI, as defined by an International Working Group (IWG)⁴⁵ to cover causes including but not limited to AD. Most studies today subtype MCI into aMCI and non-amnesic MCI (naMCI) depending on whether or not memory is impaired,⁴⁶ or further into single or multiple cognitive domains without requiring memory deficits.^{11,42,47} MCI subtypes were developed with the expectation that aMCI was likely to be a transitional state between normal cognition and

AD, whereas naMCI may progress to non-AD dementia,⁴⁷ which is most likely to be vascular dementia in the elderly population.⁴⁶ In clinical trials involving patients with aMCI, more than 90% of those with progression to dementia had clinical signs of AD.^{37,48}

1.2.3 Epidemiology of MCI

About 10-20 percent of people aged 65 and older have MCI.⁴⁹⁻⁵¹ The incidence rates of MCI varied widely. A meta-analysis with nine studies indicated that the incidence of developing MCI among the general population ranged between 9.9 and 40.6 per 1,000 person-years,⁵² and incidence rate from the Aging, Demographics, and Memory Study was even higher (60.4 per 1,000 person-years).⁵³ These variations might be affected by differences in the study characteristics, such as age, sex, or disease history, or in the diagnostic criteria used for MCI and their operational definition.^{52,54}

MCI patients are at increased risk of developing AD, with an annual rate of conversion to AD of 3-10 percent in community-based populations and 10-15 percent in specialty clinics in terms of different follow-up periods of studies.^{42,43,48,55-57} The higher rates in the specialty setting may reflect the fact that cognitive impairment is typically more advanced by the time a person seeks medical attention, the heterogeneity of study subjects, or from the discrepancies in the definition of MCI in each study.^{48,52}

1.2.4 Use of biomarker testing to predict the progression from MCI to AD

AD-specific biomarkers are compounds obtained from bodily fluids or tissue, such as cerebrospinal fluid (CSF) assays, or technically derived correlates of AD pathology, such as brain imaging markers. Four neuroimaging modalities have been used to provide evidence for the presence of AD: structural magnetic resonance imaging (MRI), functional MRI (fMRI), magnetic resonance spectroscopy (MRS) and positron emission tomography (PET).⁵⁸ In addition, four CSF biomarkers have been shown to directly

reflect brain neurochemistry: $A\beta_{40}$, $A\beta_{1-42}$, total tau (T-tau) and phosphorylated tau (P-tau).⁵⁸ Findings from these tests may identify MCI patients who are at risk for more rapid progression to dementia.⁵⁹ Two categories of biomarkers have been extensively studied for their ability to discriminate between AD patients and cognitively normal controls: 1) $A\beta$ (β -amyloid), including CSF $A\beta_{1-42}$ or PET amyloid imaging, and 2) biomarkers of neuronal injury, including CSF T-tau or P-tau, hippocampal, or medial temporal lobe atrophy on MRI, and temporoparietal/precuneus hypometabolism or hypoperfusion on PET or single-photon emission computed tomography (SPECT).⁶⁰

According to the diagnostic guidelines of AD updated during the recent NIA-AA workshop,⁴ test results that include information from these two biomarker categories could be used as a conceptual criteria to assess the likelihood that MCI symptoms are due to the underlying pathophysiology of AD.⁴⁸ When biomarkers in both $A\beta$ and neuronal injury categories are positive, there is high likelihood that MCI symptoms are due to AD. In other words, these biomarkers reflect the AD pathophysiological process in an individual with MCI, which implies that detection of MCI patients with positive biomarkers can predict a higher rate of cognitive and functional progression to AD as compared with MCI patients whose biomarkers are defined as negative.⁶⁰ Given the current lack of standardization among the techniques and the lack of agreement on cut-off thresholds for identifying high-risk groups,⁴⁸ these biomarker measures are not yet used in routine clinical care.

It is known that CSF tau and $A\beta_{1-42}$ show promise in discriminating AD from healthy controls.⁶¹ Patients with low levels of $A\beta_{1-42}$ and elevated levels of tau protein in CSF are significantly more likely to be diagnosed as AD than patients without this profile,^{57,62} although different studies use different cut-offs for abnormal findings. Furthermore, the ratio of tau(s) (the indicator of neuronal injury) to $A\beta_{42}$ has also been shown to have good discriminative ability. be highly predictive of cognitive decline in

cognitively normal cohorts as well as individuals with MCI (odds ratio, 18.1; 95% confidence interval [CI], 9.6-32.4) or very mild dementia.^{60,63}

With the promise of discriminative ability of CSF biomarkers on AD patients versus healthy controls and the challenges to define a universal cut-off value of biomarker levels, I investigated the potential of using CSF biomarkers (including biomarkers from both A β and neuronal injury categories) as a combination to develop a composite score to predict the risk of progression to AD from MCI in this thesis.

1.2.5 Currently available treatments for MCI patients

At present, no medication intended for the treatment of MCI patients has been approved by the Food and Drug Administration (FDA), although a few studies have been conducted to examine the pharmacological treatment of MCI patients. A well-designed and high-quality RCT evaluating the effect of donepezil on the progression from MCI to AD showed that hazard ratios were lower in the donepezil group compared with the placebo group during year 1 (0.42, 95%CI: 0.24-0.76) and during years 1 and 2 (0.64, 95%CI: 0.44-0.95), but not statically different during the entire three years of the study (0.8, 95%CI: 0.57-1.13).³⁷ Several systematic reviews of the use of ChEIs on MCI patients produced indeterminate results. Diniz et al.⁶⁴ found the RR of progression to dementia to be 0.75 (95% CI, 0.66 to 0.87) in those treated with a ChEIs compared to the placebo group, whereas Raschetti et al.⁶⁵ showed no significant reduction of the progression to AD. Similarly, examining the same RCTs as Diniz et al.,⁶⁴ Sobów et al.⁶⁶ concluded that ChEIs were associated with a reduction of risk of conversion to dementia of approximately 20% (odd ratio =0.8, 95%CI: 0.6-0.9) but with considerable concerns regarding a substantially increased risk of adverse events and drug discontinuation. More recently, a Cochrane review²⁶ reported the treatment effectiveness of ChEIs as RRs on delaying the progression from MCI to AD were either borderline significant or

significant for the first year (0.69; 95%CI, 0.47-1.00), the first two years (0.67; 95% CI, 0.55-0.83), respectively or the overall 3 years (RR=0.84; 95%CI, 0.70-1.02). The authors concluded that there was modest evidence that ChEIs affect progression to AD in people with MCI. This discrepancy may result from the different RCTs included in the pooled analysis of that systemic review.

1.3 Decision analysis

Decision analysis has been used for many years as a framework for evaluating the tradeoffs inherent in clinical decisions. First, a decision-analytic model is conceptualized that describes the sequence of possible consequences associated with alternative actions and assigns probabilities for those consequences and values for all of the possible outcomes. Evidence about the relative costs, risks, harms, and benefits of multiple alternatives faced by a certain patient group can be incorporated into this framework to assist decision makers in determining the best use of scarce healthcare resources. In this dissertation, we used this method based on several rationales suggested by Drummond et al.⁶⁷ First, decision analysis allows for indirect comparison between all comparators that may be unfeasible and costly in an experimental trial setting. Second, it allows for the combination of evidence from disparate sources. Third, it allows for evaluating long-term outcomes, which would again be unfeasible, costly and delay decisions if assessed in experimental trials, but are important for decision making. Finally, decision models allow us to conduct sensitivity analyses not only to test the assumptions in the model but also to explore what uncertainties are most influential on the results.⁶⁷

1.3.1 Domains of informational value from testing

Conducting diagnostic, screening, or predictive tests provide clinical value primarily because of their ability to change clinical outcomes. For example, if a patient would not be treated without the test being done but would be treated when the test is positive (and the treatment provides a net benefit for the patient), then the value of testing can be quantified by the difference in outcomes with vs. without the test. Some have argued that tests can provide value in addition to changing health-related outcomes, such as providing reassurance to patients or physicians that a serious disease is absent, the risk

of developing a disease in the subsequent years (predictive tests) or knowing for the sake of knowing.⁶⁸⁻⁷¹ Berwick and Weinstein categorized the way people value information from tests into four domains based on whether the information is valued by the physician (medical) or the patient and their family (non-medical), and whether the information is used to make decisions (decisional) or is valued for knowledge sake only (non-decisional).⁶⁹ For physicians, the information with decisional value is the information that has impact on their decision, such as the choice of medications or the choice to treat or not (i.e., the conventional decision-analytic framework). The information with non-decisional value is when the result from a test would not lead directly to a medical decision but acts to reassure the physician about their diagnosis about a disease. The information for patients with decisional value would impact their personal planning, such as financial or family planning that may differ depending on the test information. In addition, patients may worry about those who might gain access to the test results, such as an insurance company or employer, and would use this information against patients' well-being. Owing to this concern, patients might not be willing to undergo testing at all and thus there would be a loss of potential value of testing for these patients. The non-decisional value to the patient may represent the anxiety about the disease or peace of mind that comes with a favorable result.

Not only do physicians make treatment decisions based on test results and the consultation with patients themselves, but patients who learn about their disease status or risk of developing a disease from test results may also make decisions that influence the quality of life or financial status of themselves and their families. Conceptually, we can quantify the value of a test result as the potential change in outcomes associated with actions taken by physicians or patients, though the latter is more difficult in practice. In addition, it has been found that test information that is not used at all in decision making can still have value for physicians and patients.^{68,69} Studies have shown that

value may be attached to a test that provides information without helping patients or physicians make intervention decisions.⁷⁰ Berwick and Weinstein found that insured pregnant women would be willing to pay \$169 out of pocket for an ultrasound test to obtain information that is of no decisional use.²² Another recent study also showed that patients would be willing to pay \$109 to \$263 for a predictive test with no available treatment²³ (no decision possible), such as a genetic testing to predict whether persons will eventually develop AD.⁷¹ The framework of my thesis focus only on the value associated with making medical-related decisions.

1.3.2 Economic evaluation of early identification of MCI and AD

A few studies have modeled diagnostic strategies for AD patients to examine the effectiveness of early assessment and interventions,⁷²⁻⁷⁵ but few of them focus on the prodromal stage of AD.⁷⁶ A United Kingdom-based simulation model showed that identifying patients in the early stage by the assessment of MMSE could produce downstream cost savings and health benefits compared with no early assessment.⁴⁰ These findings are consistent with several US-based simulation modeling results of the potential benefits of early AD detection, through screening individuals aged 65 and over in the various primary care settings followed by treatment.^{72,76} Furthermore, by comparing several biomarker instruments (florbetaben PET or MRI) on the early diagnosis of AD, combined with a hypothetical treatment, MCI treatment on AD patients would lead to net discounted cost savings of \$11,086 per patient over their lifetime in direct medical care and \$303 in caregiver time, respectively.⁷⁴

Delaying the transition from MCI to AD may result in economic benefit.^{77,78} Results of a cost-effectiveness analysis using the genetic testing for the presence of apolipoprotein (APOE) e4 allele in MCI patients for early intervention showed that treating MCI patients with a positive test result with donepezil may be economically

attractive with an incremental cost-effectiveness ratio of Can\$38,016 per quality-adjusted life year (QALY).⁷⁹ That study assumed that donepezil does not delay cognitive decline after three years of treatment and no further treatment was provided even if patients had develop AD. Those who received donepezil have a higher rate of progression to AD in the fourth year than those who do not receive donepezil. Thus, these two groups would have an equivalent cumulative probability of developing AD by the end of year 4. After year 4, all groups have the same annual probability of developing AD.

1.3.3 Value of information analysis

Decisions based on existing evidence are associated with uncertainty in model parameters and thus there is always a chance that a “wrong” decision is made, which in turn has health and cost consequences. Value of information (VOI) analysis is an approach using Bayesian updating methods to estimate if the chance of making a wrong decision is high enough, and if the magnitude of the health and cost consequences are great enough, to support conducting new research to reduce our uncertainty surrounding all or a subset of the model parameters.⁸⁰ In the conventional framework of decision analysis, the optimal choice between two or more strategies is the one with the highest expected value.⁸¹ Expected values are based on the best available data, which may be imprecise. The result generated is referred to as the expected value given current information. The underlying uncertainty in the data introduces the possibility that a decision made based on current information is incorrect. However, if we were clairvoyant then the optimal decision could be made under all possible values for the parameter sets that incorporate parameter uncertainty.

1.4 Specific aims of my dissertation

In 2009 the NIA-AA convened three workgroups^{4,7,12} to explore the need for new diagnostic criteria that better reflect the full continuum of AD. All of the recommendations incorporate the use of biomarker information.⁷ They also suggested that it would be optimal to treat individuals with subtle evidence of cognitive impairment so as to delay the onset of overt clinical symptoms.⁷ Several CSF biomarkers can provide estimates of the risk of developing AD among patients with MCI. My study aims to address the following questions:

1. How is the risk level of MCI patients on the progression to AD defined by CSF biomarkers?
2. What is the optimal strategy to identify and intervene on MCI patients at high risk for AD?
3. What is the value of eliminating uncertainty to inform the question of early identification and treatment of MCI patients?

The overall objective of my thesis is to explore the application of cost-effectiveness analysis to assess the use of CSF biomarker testing to identify and subsequently treat MCI patients who are at increased risk of developing AD.

The three papers of my dissertation address the following specific aims lined to the three questions above.

1. Build a risk-stratification model that describes the progression from MCI to AD according to baseline CSF biomarker results.
2. Conduct a cost-effectiveness analysis (using a decision-analytical model) of treatment strategies for MCI patients with and without CSF biomarker testing.

3. Conduct a VOI analysis to estimate the potential value of eliminating or reducing the parameter uncertainty in our decision-analytical model (paper 2).

Risk stratification of MCI patients using CSF biomarker levels could be useful in selecting the appropriate interventions. In my first paper I first developed a prediction model to estimate the risk of progression from MCI to AD based on MCI patients' CSF biomarker level. In my second paper I developed a decision-analytic model to conduct a cost-effectiveness analysis of CSF biomarker testing with subsequent treatment positive findings for patients with MCI. In my third paper I conducted a VOI analysis to estimate the societal value of reducing parameter uncertainty surrounding the decision model through further research.

Of note, the MCI applied in my thesis specifically refers to aMCI, which was designed primarily to detect prodromal AD (Petersen criteria),^{42,46,47} because the symptoms of patients with aMCI are more likely to be AD-induced. Furthermore, the RCT conducted by Petersen et al., (Petersen 2005 NEJM), produced the most favorable results of the donepezil treatment effect with aMCI patients as study subjects.

1.4.1 Policy implications

A question raised by patients with MCI and their family members concerns the likelihood and time course of progression to AD. The potential benefits of early identification, such as interventions or life planning, to patients, caregivers, and society are unknown. Early detection may provide patients and their families an opportunity to plan for the future while the affected individual is still able to participate in the decision-making process.⁸² Biomarker testing may allow us to predict MCI patients' risk of developing AD and select the appropriate intervention given their risk levels, including pharmacological and/or non-pharmacological therapeutic approaches. During this early stage, an effective treatment

may be beneficial because the cognitive function might be preserved at the highest possible level for an extended time.

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Chapter 2. Risk Stratification Using CSF Biomarkers in Patients with Mild Cognitive Impairment: An Exploratory Analysis

Brief overview

Background: Cerebrospinal fluid (CSF) biomarkers can distinguish Alzheimer's disease (AD) patients from normal controls; however, their interpretation and potential for use in patients with mild cognitive impairment (MCI) remains unclear.

Objective: To examine whether biomarker levels allow for risk stratification among MCI patients who are at increased risk to develop AD, thus allowing for improved targeting of early interventions for those whose risk are higher.

Methods: We analyzed data from the Alzheimer's Disease Neuroimaging Initiative on MCI patients (N=195) to estimate their risk of developing AD for up to 6 years on the basis of baseline CSF biomarkers. We used time-dependent receiver operating characteristic analysis to identify the best combination of biomarkers to discriminate those who converted to AD from those who remained stable. We used these data to construct a multi-biomarker score and estimated the risk of progression to AD for each quintile of the multi-biomarker score.

Results: We found that $A\beta_{1-42}$ and P-tau_{181p} were the best combination among CSF biomarkers to predict the overall risk of developing AD among MCI patients (area under the curve = 0.77). The hazard ratio of developing AD among MCI patients with high-risk (3rd-5th quintiles) biomarker levels was about 4 times greater than MCI patients with low-risk (1st quintile) levels (95% confidence interval, 1.93-7.26).

Conclusion: Our study identifies MCI patients at increased risk of developing AD by applying a multi-biomarker score using CSF biomarker results. Our findings may be of value to MCI patients and their clinicians for planning purposes and early intervention as well as for future clinical trials.

2.1 Introduction

Much of the focus of Alzheimer disease (AD) research has turned to the pre-dementia stages of the disease. Patients in the prodromal stage of AD, referred to as mild cognitive impairment (MCI),¹ are at increased risk of developing AD. Evidence has emerged suggesting that such individuals² are most likely to benefit from disease-modifying therapies once they become available.^{3,4}

Blood pressure and cholesterol levels provide physicians and patients with a quantification of the risk of experiencing heart disease, which can be used to inform treatment decisions. Similarly, risk stratification of MCI patients using biomarker levels could be useful in identifying higher-risk patients early in the disease course with the goal of providing early intervention. While currently available pharmacological treatments for MCI patients provide modest benefits in terms of preventing the onset of AD,⁴⁻⁷ knowledge of a patient's risk could also trigger care planning strategies for patients and their caregivers.

Several biomarkers have been proposed to facilitate an accurate diagnosis of AD during the MCI stage, such as hippocampal atrophy on magnetic resonance imaging (MRI), amyloid imaging using positron emission tomography (PET), and changes in cerebrospinal fluid (CSF).^{8,9} CSF concentration of A β ₁₋₄₂ (a biomarker of amyloid β deposition in the brain) and biomarkers of neurodegeneration, including the CSF concentrations of total tau (T-tau) and phosphorylated tau (P-tau_{181p}) proteins, are reflected in the currently proposed diagnostic criteria⁷ for AD and MCI.¹⁰

A National Institute on Aging-Alzheimer's Association (NIA-AA) workgroup proposed criteria for the specific definition of MCI due to AD by combining clinical symptoms with CSF biomarker evidence,^{7,11} denoting the presence of a positive A β biomarker and a positive biomarker of neuronal injury (T-tau or P-tau_{181p}) as a high likelihood that the MCI syndrome is due to AD. Also, the research criteria proposed at an

International Working Group (IWG) of dementia experts considered abnormalities in CSF biomarkers as one of four supportive diagnostic features of AD.¹²⁻¹⁴ Both of these groups acknowledge the importance of CSF biomarkers in informing the likelihood of the progression of AD among MCI patients.¹⁵

Decreased levels of A β ₁₋₄₂, and elevated levels of T-tau or P-tau_{181p} in CSF have been established as useful indicators for early AD diagnosis.¹⁶⁻¹⁹ Although there have been several possible cut-off values proposed,^{5,20-22} there is a lack of agreement on cut-off thresholds due to the variability in CSF measurements between laboratories²³ and across techniques.²⁴

Combining CSF biomarkers into a single score has been shown to better discriminate between patients with an AD diagnosis compared with healthy controls than an individual biomarker.^{16,23,25,26} Examples include the Innotest Amyloid-Tau Index (IATI) defined by the ratio $A\beta_{1-42} / (240 + 1.18 \times \text{tau})$,^{26,27} the AD-CSF-Index,^{4,16,28} and the ratios T-tau/ A β ₁₋₄₂ or P-tau_{181p}/ A β ₁₋₄₂. These proposed diagnostic algorithms, however, were constructed initially to discriminate AD patients from cognitively normal controls but not to distinguish between MCI patients who have developed AD over time and those who remained stable. We have extended this logic to assess how well a combined prognostic biomarker measured at baseline could distinguish between MCI patients who develop AD over time and those who do not.

2.2 Materials and Methods

2.2.1 Subjects

All data were obtained from the AD Neuroimaging Initiative (ADNI) database October 26, 2013 (<https://ida.loni.usc.edu>). The ADNI is a non-treatment, observational study aimed at setting standards for brain imaging and chemical biomarkers for diagnosis and treatment trials. The study was launched in 2003 and is supported by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and non-profit organizations. The study (ADNI 1) enrolled 192 patients with mild AD, 398 with MCI, and 229 with no cognitive impairment.²⁹ Six month or one year clinical, imaging, and biomarker assessments were conducted over a study period.

The primary goal of the ADNI is to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. We included MCI subjects with complete data on CSF biomarkers at study entry in our analysis (N=195). We extracted all assessments at baseline and the disease status at each follow-up.

2.2.2 CSF measurement

The methods for CSF acquisition and biomarker measurement used in the ADNI study have been reported previously.²² The CSF concentration of A β ₁₋₄₂, T-tau, and P-tau_{181p} were measured in the baseline CSF samples using Innogenetics reagents (research use only AlzBio3 immuno-assay kits, Ghent, Belgium) and the multiplex xMAP Luminex platform (Lumnix Corporation, Austin, TX) at the Penn ADNI Biomarker Core Laboratory.³⁰ This is not directly comparable with another commonly used analytical platform in European countries, the Innotech (enzyme-linked immunosorbent assay [ELISA]).¹⁸ More details on data collection of the CSF samples can be found at on the

ADNI website (www.adni-info.org).

2.2.3 Statistical analysis

To examine the presence of selection bias between MCI patients with CSF information and those without, we compared baseline demographic and clinical data between groups, using a non-parametric Kruskal-Wallis test for continuous variables and Pearson's χ^2 test for dichotomous variables.

Receiver operator characteristic (ROC) curves are standard summaries of diagnostic accuracy for continuously valued test results^{31,32} and dichotomous disease status. In our study, however, disease status is defined as the development of AD, which can change during follow-up. Accordingly, we used time-dependent ROC analysis to characterize the predictive accuracy of CSF biomarkers with continuous values and the time-dependent outcome of interest.^{31,33} Hence, we sought to characterize the prognostic accuracy of combinations of CSF biomarkers among MCI patients with potential for progression to AD and further estimate the AD risk in terms of CSF biomarker values measured at study entry. To our knowledge, this was the first study to examine the predictive accuracy of CSF biomarkers on MCI patients using time-dependent ROC analysis.

We first fit Cox proportional hazards (PH) models using time to AD as the dependent variable and $A\beta_{1-42}$, T-tau, and P-tau_{181p} as the primary independent variables to assess the discriminatory ability of these biomarkers on the progression to AD. We summarized the discrimination potential of the combinations of CSF biomarkers, measured at baseline (t=0), to distinguish between MCI patients who developed AD by a particular time t and those who remained stable by calculating ROC curves for cumulative AD cases at each follow-up time t.³¹

Using time-dependent ROC methods we derived combinations of sensitivity and specificity by comparing the predicted probabilities of developing AD (estimated from the fitted Cox PH model of CSF biomarkers mentioned above) and the actual outcomes at each follow-up time ($t = 1-6$ years). More importantly, censored observations were included in the calculation of sensitivity and specificity. For each time t , we calculated the area under the ROC curve ($AUC(t)$), which can be interpreted as the probability that a randomly selected MCI patient who developed AD at time t has a larger predicted risk than a randomly selected MCI patient who remained stable. We used $AUC(t)$ to examine the best combination of CSF biomarkers for longitudinal predictive ability for the progression of AD for MCI patients. After the most optimal combination was chosen, we used the coefficients from the fitted Cox PH model to construct a multi-biomarker score (S) for MCI patients using the following equation: $S = \sum(\beta_i \times \text{biomarker } A_i)$, where β_i denotes the estimated beta coefficients for biomarkers A_i .

We then divided MCI patients into quintiles based on their multi-biomarker scores, and computed the cumulative risk of progression to AD for each group using Kaplan-Meier methods. We compared the observed risk functions estimated from the Kaplan Meier methods graphically to those estimated from Cox PH regression methods using the same five groups of patients to assess model fit.

We then illustrated the longitudinal risk of developing AD for each quintile or risk group using Kaplan-Meier methods to establish a prediction model for MCI patients and calculate the probabilities of progression to AD by each group at each time point. We also calculated covariate-adjusted hazard ratios by incorporating potential confounding variables into the Cox PH model. The analyses were done with and without adjustment for potential confounding of age, sex, marital status, education level, apolipoprotein (APOE) $\epsilon 4$ alleles carrier status, baseline clinical dementia rating sum of boxes (CDR-

SB), baseline Mini-Mental State Exam (MMSE) score, baseline Alzheimer's Disease Assessment Scale (ADAS 13) score, baseline hippocampus volume, baseline ventricles volume, and the anti-dementia medication history. We further used a multivariate backward selection Cox regression model to estimate the impact of the potential confounders (p-values for removal from the model was defined as 0.05).

We used log-rank test to compare the risk of progression to AD among quintiles. The proportional hazards assumption was assessed using the log (-log) plots of the survival function using Schoenfeld residuals.³⁴ The Wilcoxon (Breslow–Gehan) test was performed when hazard functions are thought to vary in ways other than proportionally. Risk groups were collapsed if no significantly different risk was presented between quintiles.

We compared the prognostic power of the multi-biomarker score to that of each individual CSF biomarker alone and to other diagnostic indices that are commonly used such as the ratio tau/ $A\beta_{1-42}$ (T-tau or P-tau_{181p}), the index described by Hulstaert et al.²⁶ computed as $A\beta_{1-42}/(240 + 1.18 \times \text{tau})$ (T-tau or P-tau_{181p}), and the AD-CSF-index developed by Molinuevo et al.¹⁶ by applying these indices on the MCI sample in our study and then computing the AUC at each time point separately by time-dependent ROC analyses described earlier. The latter two indices were constructed using AD patients and cognitively normal controls.

All the analyses were done by using Stata version 12 (StataCorp, College Station, TX) and R software (version 3.0.3; R Foundation for Statistical Computing, Vienna, Austria) with the survivalROC and risksetROC libraries.

2.3 Results

2.3.1 Descriptive statistics

In total, 195 of 398 MCI patients with complete CSF information at baseline were included (**Table 2.1**). Among those with complete CSF data, the mean age was 74 years (range: 67–81 years old), the majority of the sample was men (67%), about 70% received no anti-dementia medication at study entry, 2.5% received either cholinesterase inhibitors (ChEIs) or memantine, and the rest had no information available. The median follow-up period was 30 months (range, 9–58 months). With the mean conversion time of 24.5 months, 102 out of 195 MCI patients have converted to AD. The cumulative risk of developing AD by 6 years was 66%, which is similar to previous studies where 80% of MCI patients developed AD within 8 years.³⁵ No significant differences were found between MCI patients with and without complete CSF biomarker information at baseline (**Table 2.1**). (**Appendix 2.A** presents demographic characteristics of MCI patients with CSF information between those who have converted to AD and those who remained stable within 6 years).

2.3.2 Time-dependent ROC analysis

We assessed the discriminatory ability of CSF biomarkers by generating ROC curves at annual time points. The results of fitting a Cox PH model with the three biomarkers showed that $A\beta_{1-42}$ and P-tau_{181p} were significantly associated with the risk of developing AD (**Appendix 2.B**). Furthermore, the time-dependent ROC analyses showed no difference between the AUC(t) values using the combination of all three CSF biomarkers compared with the combination of $A\beta_{1-42}$ and P-tau_{181p} only (the AUCs were 0.65 and 0.77 for year 3 and year 6, respectively, regardless of whether T-tau was included or not). The combination of $A\beta_{1-42}$ and P-tau_{181p} discriminated reasonably well among those MCI patients who developed AD during follow-up and those who remained stable

(**Figure 2.1**). The AUC(t) values ranged from 0.61 at 2 years to 0.77 at 6 years. Accordingly, we chose $A\beta_{42}$ and P-tau_{181p} to construct the multi-biomarker score in patients with MCI.

2.3.3 Predictive discrimination of CSF multi-biomarker score

We calculated a multi-biomarker score for each MCI patient using the coefficients derived from the Cox PH model. The score was calculated as $(-0.006) \times A\beta_{1-42} + 0.012 \times P\text{-tau}_{181p}$. The mean multi-biomarker score was -0.56 ± 0.49 , and the distribution of the scores appeared to be bimodal (**Appendix 2.C**). We divided MCI patients into quintiles according to their multi-biomarker score and then estimated the hazard ratio of the progression to AD for each quintile relative to the first quintile group (**Table 2.2**), controlling for the baseline risk factors listed in **Table 2.1** (the result of fitting initial three CSF biomarkers and other baseline risk factors is presented in **Appendix 2.D**). Among the covariates considered, only ADAS 13 score and hippocampus volume showed significant impact on the progression to AD.

The univariate Cox PH model showed a significant difference in the probability of progression from MCI to AD between quintiles of the multi-biomarker score (**Table 2.3**). We found that MCI patients with a biomarker score in the third quintile had the highest risk of developing AD when adjusting for demographic or MRI imaging variables but not cognitive tests. In unadjusted analyses, those with a biomarker score in the fifth quintile appeared to have the highest risk.

We compared the observed risk of progression to AD by quintiles of the multi-biomarker score using Kaplan-Meier survival methods (i.e., the cumulative risk of developing AD is 1 minus the Kaplan-Meier estimate for the proportion of MCI patients remaining stable at time t). The cumulative risk of developing AD by 6 years associated with multi-biomarker scores in the 1st through 5th quintile were 33%, 50%, 71%, 81%,

and 90%, respectively (the log-rank test, p -value <0.0002 ; the Wilcoxon test, p -value <0.0004). We compared the observed Kaplan-Meier survival curves graphically with those predicted by the Cox PH model when using the same quintile groups of biomarker scores in order to assess model fit (not shown). The model exhibited good fit with the 6-year risk of developing AD- risk increasing monotonically as the multi-biomarker score increased, and the proportional hazard assumption was not violated (p -value = 0.24).

We found a clear gap between the group of the third, fourth, and fifth quintiles and the first and second quintiles (**Figure 2.2A**), and we found no significantly different risk among the top three quintiles by either the log-rank tests or the Wilcoxon (Breslow–Gehan) test. Thus, we further collapsed the top three quintiles and labeled this group as high risk, we labeled the second quintile as intermediate risk and the first quintile as low risk. We then estimated the longitudinal variation of cumulative risk on the progression to AD (**Figure 2.2B**), which showed the clear classification of AD risk by multi-biomarker scores categorized as three risk levels (high, intermediate, and low) with a follow-up of up to 6 years. The univariate Cox PH model using these three risk groups showed a significant difference in the probability of progression from MCI to AD (**Table 2.4**). The unadjusted hazard ratio of developing AD among MCI patients with high-risk biomarkers levels was about 4 times greater than MCI patients with low-risk levels (95% confidence interval [CI], 1.93-7.26), whereas the hazard ratios were 3.5, 2.8, and 2.5 respectively when controlling for demographic, cognitive test, and MRI imaging covariates.

The multivariate backward selection model results indicated that CDR-SB, ADAS13 and hippocampus volume were significantly associated with the progression to AD in patients with MCI, considering all baseline covariates simultaneously. Other risk factors, such as APOE ϵ 4 carrier status and MMSE score did not contribute to the explanatory power of the model. However, the hazard ratio for high-risk biomarker levels was only about 2 times greater than low-risk levels and was only borderline significant

(95% CI, 0.97-4.38) when we adjusted for three significant covariates selected from the multivariate backward selection analysis (**Table 2.4**).

2.3.4 Comparison of discrimination power

Table 2.5 presents the AUC values at year 3 and year 6 of the time-dependent ROC analyses applying several combinations of biomarkers as well as several published indices^{16,26} on the MCI sample in our study. We found no difference in AUC values at year 3, whereas AUC values ranged from 0.69 to 0.77 at year 6 (although these results were similar). We found that the multi-biomarker score estimated in our study on MCI patients and the AD-CSF-index (P-tau) developed by Molinuevo et al.¹⁶ that compared AD patients to healthy controls were associated with the best AUC value at year 6 among all tested diagnostic indices that predicted the longitudinal progression to AD. Specifically, their discriminative power between MCI patients who converted to AD and those who remained stable were 0.77 at year 6. With regards to the remainder of the indices, combined biomarkers presented better discriminative ability (higher AUC) than individual CSF indices.

2.4 Discussion

Our study sought to enhance the estimation of probability of progression from MCI to AD by creating a biomarker-based prognostic index. We found that a combined multi-CSF biomarker score, as categorized using quintiles or risk levels, provides a good estimate of the risk of developing AD up to 6 years. The hazard ratio of developing AD among MCI patients with high-risk biomarker levels was about 4 times greater than MCI patients with low-risk levels (95% CI, 1.93-7.26). Furthermore, the result of applying our index on AD patients and healthy controls from ADNI 1 (N=216) showed the similar cut-off values of quintiles of multi-biomarker scores as those from MCI patients (**Appendix 2.E**).

In our case, the combination of $A\beta_{1-42}$ and P-tau_{181p} showed predictive results similar to the combination of all three CSF biomarkers together, which may due to P-tau_{181p} and T-tau status as neurodegeneration markers. We estimated the AUCs of published diagnostic indices developed from AD patients and healthy controls by applying those indices to our MCI sample and compared them with the AUC estimated with our index. The multi-biomarker score of combing $A\beta_{1-42}$ and P-tau_{181p} together showed better and comparable discriminative abilities than those relying on single CSF biomarker and published indices,^{4,16,26,36} respectively (**Table 2.5**). However, diagnostic indices developed in the previous studies,^{4,16,26,36,37} may not be applicable to the current study since our index was designed based on the MCI population, whereas the former indices were based on comparisons between AD patients and healthy controls. The interpretation of any comparative results should be made with caution due to the heterogeneity of the study populations used in each study.

We demonstrated that the multi-biomarker score using the ADNI dataset with the Luminex-xMAP analytical platform resulted in AUCs and discriminative ability similar to those diagnostic indices developed using CSF biomarkers analyzed from different platforms or assays (ELISA or mesoscale) applied on AD patients versus healthy

controls.^{4,16,26,27} Moreover, our study used a time-dependent ROC method, which is able to capture censored observations in the calculation of sensitivity and specificity better than a logistic regression model used in other studies. This approach allowed us to accurately evaluate the discriminative capacity of CSF biomarkers measured at baseline over time.

It is well known that decreased $A\beta_{1-42}$ and elevated tau levels predict progression from MCI to AD,^{18,38-41} but there is a lack of the agreement regarding potential cut-off thresholds.²⁴ In other words, individuals with MCI who exhibit low levels of $A\beta_{1-42}$ and high levels of T-tau or P-tau_{181P} have higher risk of developing AD compared to those with higher levels of $A\beta_{42}$ or lower levels of T-tau or P-tau_{181P}, but the relationship between quintiles of our index derived from CSF biomarker concentration level and the progression of AD on MCI patients might not be ordinal. While the unadjusted data for quintiles showed that MCI patients with the composite biomarker score at the top quintile had a highest risk, we found that MCI patients with the score at the middle quintile tended to have a higher risk of developing AD after adjusting for MRI imaging (hippocampus volume and ventricles volume), which was shown to be a good predictor of MCI to AD conversion.^{42,43} This might be attributable to the heterogeneity of the study population as well as the discrepant continuum between the pathophysiological process of AD and its clinical symptomatology, as studies have shown that altered $A\beta$ metabolism precedes tau-related pathology, neuronal degeneration, and clinical symptoms.^{44,45} It is also unclear if the APOE genotype influences the CSF biomarkers-based risk classification of AD in some studies^{4,46}; however we found no significant difference of APOE $\epsilon 4$ carrier status by quintile/risk level groups and no significant interaction between APOE $\epsilon 4$ carrier status and quintiles of multi-biomarker scores using Cox PH model. Validation in a larger sample would be informative in this regard.

The consensus from the Alzheimer's Biomarkers Standardization Initiative (ABSI) is to consider CSF biomarker analysis as a routine clinical test in patients with early-onset dementia, either at the prodromal stage or with atypical AD.⁴ With a low frequency of complications for lumbar puncture,⁴⁷ especially in the elderly population,^{48,49} routine analysis of CSF as part of the clinical workup for patients with possible AD has been advocated.^{6,50,51} In addition to pharmacological treatments, other interventions, such as cognitive rehabilitation or participation in social activities, are also recommended for MCI patients.⁵² Several cognitive interventions, such as cognitive stimulation, cognitive training, and cognitive rehabilitation have shown some effect on improving learning abilities and cognition among MCI patients.⁵³ Thus, properly selecting candidates for earlier treatment is necessary. Our results showed that MCI patients in the 3rd, 4th, and 5th quintiles of multi-biomarker score (the high-risk group) were most likely to convert to AD, which should qualify them as the primary target population if initiating a treatment program MCI patients was applicable. The multi-biomarker score developed in our study using an MCI population constitutes a reasonable measure with regard to the risk stratification of MCI patients for targeted interventions, such as potentially effective treatments or life management strategies. Furthermore, cost-effectiveness analysis for CSF biomarkers and subsequent interventions could be performed to show the utility of our risk stratification approach to payers as suggested by the ABSI⁴ by targeting different intervention strategies based on the risk level determined by the multi-biomarker score here (with accurate diagnosis of MCI as the premise).

There are limitations to our study. First, neither the baseline biomarker level when cognitively normal persons develop MCI nor the disease history of MCI patients was known. This might resulted in the non-ordinal risk pattern by quintiles of multi-biomarker score. It is also possible that the MCI subjects (late MCI)^{54,55} recruited in the first phase of the ADNI were nearing progression to AD, and their biomarker levels were

close to the threshold of AD. Further validation studies should be applied on a population with relatively early stage of MCI, such as early MCI defined in the second phase of ADNI (i.e., objective memory loss documented with scores approximately 0.5-1.5 SD below the mean of healthy controls on delayed paragraph recall performance from the Wechsler Memory Scale Logical Memory II),⁵⁶ to fully describe the continuum of CSF biomarker levels and the disease progression of MCI for better discriminatory performance if possible. Second, changes in the concentrations of CSF tau and $A\beta_{1-42}$ are early events in the pathogenesis of AD and levels of $A\beta_{1-42}$ are already fully decreased at least 5 to 10 years before conversion to AD, whereas T-tau and P-tau_{181p} seem to act as later markers.^{45,57} This means that patients with MCI may not be an optimal target population to apply the CSF analysis since CSF biomarkers (especially $A\beta_{1-42}$) convert to pathologic values several years before the first appearance of clinical signs.⁶ Finally, the current results demonstrate that the discriminatory accuracy of the composite biomarker model is not yet clinically satisfactory with an insufficient sample size and the heterogeneity of study samples.

2.5 Conclusion

In summary, our study examined the feasibility of distinguishing MCI patients with higher risk of developing AD from those at lower-risk through the creation of a multi-biomarker score. We did not attempt to define a universal cut-off value on CSF biomarker concentration levels, which would be difficult due to assay platforms generating different absolute values²⁴ and intra-center or inter-center variability of CSF concentration level.⁵⁰ However, we did find similar cut-off results of our index, derived from MCI patients, applying on AD patients and healthy control. Our findings demonstrate that MCI patients could be effectively categorized into different risk groups of developing AD through the use of multiple CSF biomarkers, thus potentially identifying persons with MCI who are best suited for pharmacological or non-pharmacological treatment.

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Table 2.1 Demographic characteristics of the Alzheimer’s disease Neuroimaging Initiative (ADNI 1) MCI subjects with and without complete CSF biomarker information at baseline.*

Covariate	With CSF data (n=195)	Without CSF data (n=203)	P-value
Demographic factors			
Age, mean + SD, y	74 ± 7	75 ± 7	0.16
Male, %	66.7	62.6	0.39
Education, mean + SD, y	16 ± 3	15 ± 3	0.43
Marital status, %			0.12
Married	84.1	76.4	
Widowed	9.2	14.8	
Divorced	6.2	6.4	
Never married	0.5	2.5	
With Family history of dementia, %	4.6	2.0	0.14
APOE ε4 carrier, %	53.8	52.7	0.82
Baseline cognitive test, mean + SD			
MMSE score	26.91 ± 1.79	27.14 ± 1.76	0.33
CDR sum of boxes	1.56 ± 0.89	1.64 ± 0.89	0.90
ADAS 13	18.85 ± 6.23	18.45 ± 6.32	0.41
Anti-dementia medications history, %			0.65
None	70.3	54.7	
ChEI only	1.0	1.5	
Memantine only	1.5	2.0	
NA	27.2	41.9	
Baseline MRI volumetric measures			
Hippocampus volume (mm ³)	6,355 ± 1,085	6,448 ± 1,077	0.86
Ventricles volume (ml)	43,751 ± 24,574	44,266 ± 24,876	0.60

*No significance different was found in terms of covariates listed above between MCI patients with and without complete CSF biomarker information.

Abbreviation: MCI, mild cognitive impairment; APOE, apolipoprotein E; MMSE, Mini-Mental State Examination; CDR-SB, Clinical Dementia Rating–sum of boxes subscale; ADAS-cog, AD Assessment Scale–cognitive subscale; MRI, magnetic resonance imaging; ChEI, cholinesterase inhibitor; SD: standard deviation; NA, not available.

Table 2.2 Hazard ratio of each covariate using the Cox proportional hazards model.*

Covariate	HR	SE	P-value
Multi-biomarker score in the ^a			
2nd quintile	1.82	0.86	0.206
3rd quintile	2.24	1.03	0.078
4th quintile	1.79	0.80	0.194
5th quintile	1.63	0.81	0.327
Age	0.97	0.02	0.125
Male	1.02	0.34	0.949
Education	0.99	0.04	0.850
Married (reference)			
Widowed	0.81	0.39	0.664
Divorced	1.63	0.94	0.394
Never married	3.82	4.21	0.224
Having family history of dementia	0.76	0.39	0.591
APOE ε4 carrier	1.21	0.33	0.491
Baseline MMSE score	0.95	0.08	0.501
Baseline CDR sum of boxes	1.29	0.19	0.085
Baseline ADAS 13	1.09	0.03	0.001
Baseline hippocampus volume (mm ³)	0.999566	0.00	0.005
Baseline ventricles volume (ml)	1.000003	0.00	0.628

*N=148.

^aQuintiles were defined by the equation: $(-0.006) \times A\beta_{1-42} + 0.012 \times P\text{-tau}_{181p}$.

Table 2.3 Proportional hazards model results of patients with MCI by quintiles of multi-biomarker scores.*

Quintile of multi-biomarker scores	Adjusted									
	Unadjusted		demographic ^a		cognitive test ^b		MRI imaging ^c		backward selection ^d	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
1st quintile (reference group)										
2nd quintile	1.93	0.86-4.35	1.94	0.85-4.44	1.63	0.70-3.78	2.10	0.85-5.16	2.03	0.84-4.92
3rd quintile	3.82	1.83-7.99	3.73	1.74-8.02	1.24	1.41-6.79	2.73	1.17-6.33	2.43	1.03-5.71
4th quintile	3.40	1.64-7.05	3.21	1.49-6.92	2.41	1.11-5.25	2.37	1.03-5.44	1.94	0.85-4.43
5th quintile	4.10	1.97-8.54	3.73	1.69-8.24	3.03	1.39-6.62	2.44	1.05-5.64	1.93	0.83-4.47

*The included covariates in each adjusted categories are listed in Table 2.1.

^aCovariates included age, sex, education level, marital status, and APOE ε4 carrier status.

^bCovariates included baseline MMSE, baseline CDR sum of boxes, and baseline ADAS 13.

^cCovariates included baseline hippocampus volume and baseline ventricles volume.

^dCovariates included baselines CDR-SB, baseline ADAS13 and baseline hippocampus volumes. *P*-value for removal from the model was defined as 0.05.

Table 2.4 Relationship between baseline covariates and the risk of developing AD in patients with MCI.

Risk level ^e	Adjusted									
	Unadjusted		demographic ^a		cognitive test ^b		MRI imaging ^c		backward selection ^d	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Low (reference group)										
Intermediate	1.93	0.86-4.35	1.93	0.85-4.42	1.63	0.70-3.79	2.08	0.85-5.11	2.02	0.83-4.91
High	3.75	1.93-7.26	3.53	1.75-7.12	2.8	1.38-5.71	2.5	1.18-5.31	2.06	0.97-4.38

*The included covariates in each adjusted categories are listed in Table 2.1.

^aCovariates included age, sex, education level, marital status, and APOE ε4 carrier status.

^bCovariates included baseline MMSE, baseline CDR sum of boxes, and baseline ADAS 13.

^cCovariates included baseline hippocampus volume and baseline ventricles volume.

^dCovariates included baselines CDR-SB, baseline ADAS13 and baseline hippocampus volumes. *P*-value for removal from the model was defined as 0.05.

^eThe lowest quintile is labeled low risk, the second quintile is labeled intermediate risk, and the top three quintiles are labeled high risk.

Table 2.5 Prognostic power of the AD indices based on CSF biomarkers by time-dependent ROC analysis.

Index	AUC					
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
A β ₁₋₄₂	0.58	0.60	0.63	0.66	0.68	0.74
P-tau _{181p}	0.63	0.61	0.65	0.68	0.72	0.72
T-tau	0.54	0.61	0.65	0.68	0.68	0.69
P-tau _{181p} /A β ₁₋₄₂	0.63	0.62	0.65	0.70	0.74	0.76
T-tau/A β ₁₋₄₂	0.57	0.62	0.66	0.70	0.70	0.73
Hulstaert (P-tau), A β ₁₋₄₂ /(240+1.18 x P-tau _{181p}) ^{a, 26}	0.60	0.60	0.64	0.68	0.71	0.75
Hulstaert (T-tau), A β ₁₋₄₂ /(240+1.18 x T-tau) ^{a, 26}	0.58	0.61	0.66	0.69	0.70	0.74
AD-CSF-index (P-tau _{181p}) ^{a,b, 16}	0.63	0.62	0.66	0.70	0.74	0.77
AD-CSF-index (T-tau) ^{a,b, 16}	0.57	0.62	0.66	0.70	0.71	0.74
Current study ^c	0.62	0.62	0.65	0.70	0.74	0.77

^aIndices were derived from AD patients versus healthy controls.

^b $\frac{A\beta_{1-42} - A\beta_{\text{minimum}}}{A\beta_{\text{maximum}} - A\beta_{\text{minimum}}} - \frac{\text{tau} - \text{tau}_{\text{minimum}}}{\text{tau}_{\text{maximum}} - \text{tau}_{\text{minimum}}}$. tau was referred to either P-tau_{181p} or T-tau in this case.

^c $(-0.006) \times A\beta_{1-42} + 0.012 \times \text{P-tau}_{181p}$.

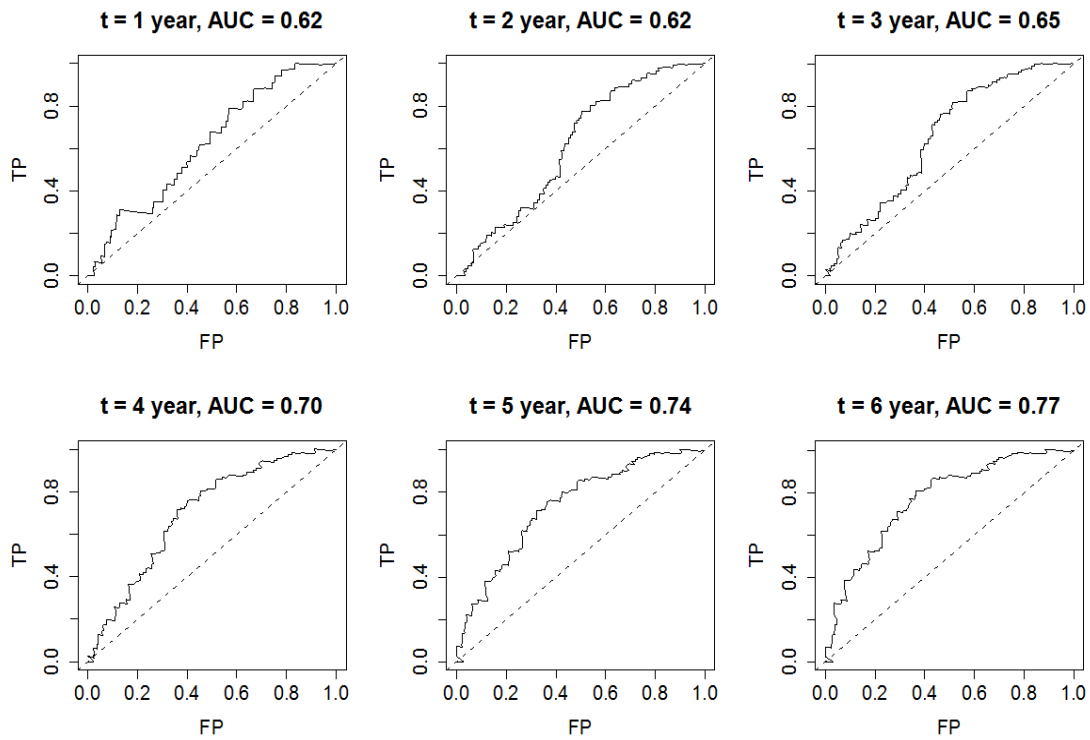


Figure 2.1 Time-dependent ROC curves by follow-up period and the combinations of CSF biomarkers ($A\beta_{1-42}$ + P-tau181p) estimated from a Cox proportional hazards model. TP: true positive = sensitivity; FP: false positive = 1-specificity.

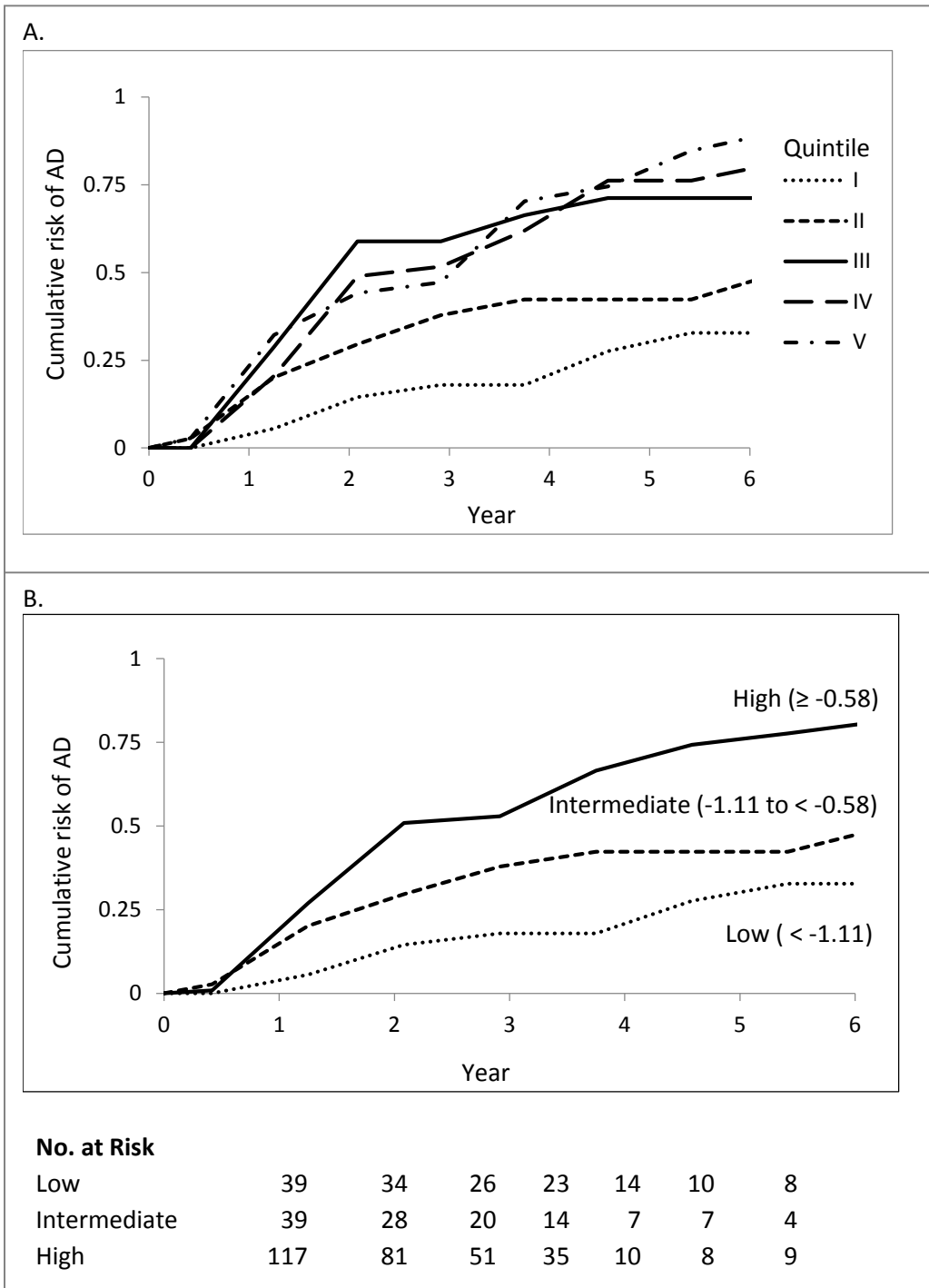


Figure 2.2 Cumulative probability of AD, according to quintile of multi-biomarker scores (Panel A) and risk levels (Panel B). Multi-biomarker scores were classified as low (1st quintile), intermediate (2nd quintile), or high (3rd, 4th, and 5th quintiles). The parenthesis presented the range the multi-biomarker scores by risk levels.

Appendix 2.A The demographic characteristics of converters vs. non-converters among MCI patients with CSF biomarker information.

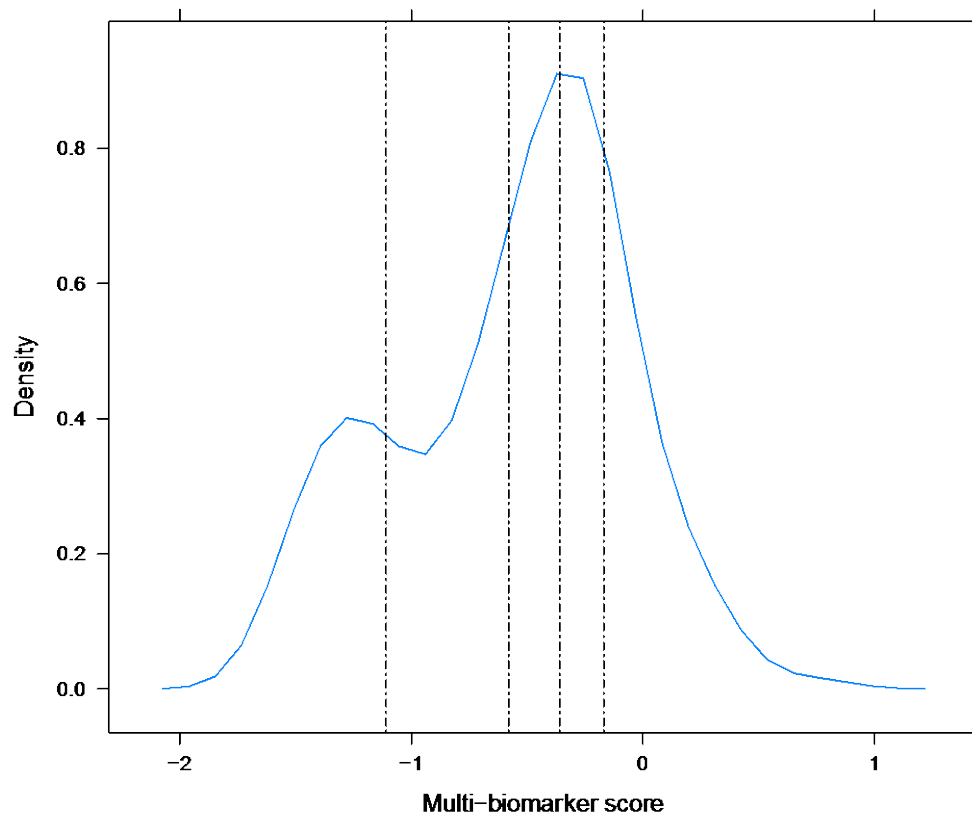
	Converter (n=102)	Non-converter (n=93)	P-value
Demographic factors			
Age, mean + SD, y	74 ± 7	75 ± 7	0.56
Male, %	62.7	71.0	0.22
Education, mean + SD, y	16 ± 3	16 ± 3	0.89
Marital status, %			0.68
Married	84.1	85.3	
Widowed	9.2	8.8	
Divorced	4.9	7.5	
Never married	1.0	0.0	
With Family history of dementia, %	6.9	2.2	0.12
APOE ε4 carrier, %	61.8	45.2	0.02
Baseline cognitive test, mean + SD			
MMSE score	26.62 ± 1.76	27.23 ± 1.78	0.02
CDR sum of boxes	1.76 ± 0.94	1.35 ± 0.77	0.00
ADAS 13	20.71 ± 5.61	16.86 ± 6.28	0.00
Anti-dementia medications history, %			0.90
None	71.6	68.8	
ChEI only	1.0	1.1	
Memantine only	2.0	1.1	
NA	25.5	29.0	
Baseline MRI volumetric measures			
Hippocampus volume (mm ³)	5,978 ± 998	6,781 ± 1,025	0.00
Ventricles volume (ml)	45,077 ± 24,312	42,258 ± 24,955	0.25

Abbreviation: MCI, mild cognitive impairment; APOE, apolipoprotein E; MMSE, Mini-Mental State Examination; CDR-SB, Clinical Dementia Rating–sum of boxes subscale; ADAS-cog, AD Assessment Scale–cognitive subscale; MRI, magnetic resonance imaging; ChEI, cholinesterase inhibitor; SD, standard deviation; NA, not available.

Appendix 2.B Cox proportional hazards model of CSF biomarkers only on predicting the progression to AD from MCI.

CSF biomarker	Coefficient	SE	<i>P</i> -value
All 3 biomarkers model			
A β ₁₋₄₂	-0.006	0.002	0.006
T-tau	-0.001	0.002	0.643
P-tau _{181p}	0.015	0.007	0.041
Best combination model			
A β ₁₋₄₂	-0.006	0.002	0.005
P-tau _{181p}	0.012	0.006	0.031

Appendix 2.C Distribution of multi-biomarker scores with the cut-off value between the 1st and the 2nd quintile as -1.11, the 2nd and the 3rd quintile as -0.58, the 3rd and the 4th quintile as -0.36, and the 4th and the 5th quintile as -0.17.



Appendix 2.D Hazard ratios of CSF biomarkers and other covariates using Cox proportional hazards model.*

Covariate	HR	SE	P-value
CSF biomarkers			
A β ₁₋₄₂	1.00	0.00	0.247
T-tau	1.00	0.00	0.351
P-tau _{181p}	1.01	0.01	0.452
Age	0.97	0.02	0.193
Male	1.04	0.34	0.897
Education	0.98	0.04	0.712
Marital status			
Married (reference)			
Widowed	0.87	0.43	0.783
Divorced	1.75	0.99	0.321
Never married	3.07	3.43	0.314
Having family history of dementia	0.65	0.37	0.443
APOE ϵ 4 carrier	1.15	0.32	0.623
Baseline MMSE score	0.94	0.07	0.438
Baseline CDR sum of boxes	1.33	0.20	0.057
Baseline ADAS 13	1.09	0.03	0.001
Baseline hippocampus volume (mm ³)	0.999571	0.00	0.005
Baseline ventricles volume (ml)	1.000004	0.00	0.564

*N=145.

Appendix 2.E Cut-off values of quintiles of using multi-biomarker scores on MCI patients versus on AD patients and healthy control of ADNI 1.

Cut-off	MCI (n=195)	AD vs. Control (n=216)
1st quintile	<-1.11	<-1.23
2nd quintile	-1.11 to < -0.58	-1.23 to < -0.81
3rd quintile	-0.58 to <-0.36	-0.81 to <-0.48
4th quintile	-0.36 to < -0.17	-0.48 to < -0.21
5th quintile	≥ -0.17	≥ -0.21

Chapter 3. Using Cerebrospinal Fluid Biomarker Testing to Target Treatment to Patients with Mild Cognitive Impairment at Increased Risk of Alzheimer's Disease: A Cost-Effectiveness Analysis

Brief overview

Objective: Certain cerebrospinal fluid (CSF) biomarkers can identify patients with mild cognitive impairment (MCI) who are at different level of risk of progression to Alzheimer's disease (AD). Knowing a patient's risk level may allow for early interventions for some of these patients. The objective of our study was to assess the costs-effectiveness of several test-treat strategies using CSF biomarker testing among MCI, compared with strategies without testing.

Methods: We developed a state-transition model to project lifetime AD-free life years, quality-adjusted life years (QALYs) and costs for a cohort of 65-year-old MCI patients under different test-treat strategies. For the test-treat strategies, we targeted treatments based on patients' risk levels of progression from MCI to AD, whereas strategies without testing included no MCI treatment (treat patients only if they convert to AD), and MCI treatment (treat MCI patients). We used data from the Alzheimer's Disease Neuroimaging Initiative to incorporate CSF biomarker level-based risk of progression to AD. Treatment effectiveness to delay the progression from MCI to AD, derived from a systematic review, was 0.84 and continued for 3 years. For AD patients with mild AD treatment effectiveness was 0.58 and persisted until patients transitioned to a severe stage. We further performed deterministic and probabilistic sensitivity analyses (PSA) to evaluate the uncertainty surrounding input parameters.

Results: The two test-treat strategies were the less effective and less costly compared to strategies without testing. The no MCI treatment strategy resulted in the highest cost and the highest QALYs with an incremental cost-effectiveness ratio of \$29,400 per QALY compared to MCI treatment. Treatment effectiveness for patients with mild AD and treatment effectiveness for MCI patients were the most important parameters in terms of CEA results. The no MCI treatment strategy was associated with 63% probability of being cost-effective in the PSA results at willingness to pay of

\$50,000/QALY. In the post-hoc analysis, the strategy of treating MCI patients at low risk was cost-effective with ICER of \$39,500/QALY compared with other four primary strategies.

Conclusion: Based on the current evidence, this study illustrates the potential for early targeted interventions for MCI patients who are at risk of developing AD, especially for those at low risk.

3.1 Introduction

Alzheimer's disease (AD) is a devastating neurodegenerative disease that impairs memory, thought, and behavior; reduces quality of life; and decreases survival. An estimated 5.2 million people in the US have AD, and it is the sixth leading cause of death.¹ As age is the most prominent risk factor for the disease, the aging of the population in the US will result in an increase to an estimated 7.7 million cases in 2030 and 11 to 16 million cases in 2050.² Patients with AD are high users of health and long-term care services. More than 15 million family caregivers who provide unpaid care for people with AD and other dementia in the US are under great psychological and physical burden. AD and other types of dementia cost Medicare \$113 billion per year and Medicaid \$37 billion per year. The total annual direct costs of AD are estimated at \$214 billion.¹

Persons with eventual AD may progress through a prodromal stage called mild cognitive impairment (MCI)³ or cognitive impairment without dementia (CIND),⁴ a stage characterized by early memory loss but with relatively well-preserved activities of daily living, before they were clinically diagnosed as AD. Patients with MCI are at increased risk for the development of AD, with an annual rate of conversion to AD of 3-10 percent in community-based populations and 10-15 percent in specialty clinics.^{3,5-9} The MCI stage of AD could provide a clinical opportunity for pharmacological intervention with the belief that it is more likely to achieve disease modification if interventions could be applied earlier in the course of AD,¹¹ or cognitive interventions, such as cognitive stimulation, cognitive training, and cognitive rehabilitation.¹² Thus, patients with MCI are a natural target population to allow proactive, comprehensive management or appropriate treatments to be initiated at an earlier disease course or milder level of cognitive impairment before the clinical diagnosis of AD.^{3,13,14}

In clinical practice, physicians order prognostic tests to obtain a better

understanding of patients' risk levels of developing a disease, and have the option to intervene if the test result shows a high risk of disease. The improvement in patients' health outcomes from early intervention due to test results, compared to no testing, provides a measure of the clinical value of the prognostic test. Specifically, the clinical value of test information can be quantified as the difference in health and economic outcomes associated with having the test information (where interventions depend on the test results) compared to not having the information (where physicians can only choose to intervene or not on everyone). Moreover, this value often depends on carefully-targeted risk-stratification, because implementation of universal treatment programs may be limited by issues of patient acceptance, cost effectiveness, insurance coverage, and treatment-related side effects. Risk-stratification holds the prospect of achieving high rates of detecting patients who are most likely to develop a disease and providing them with effective treatments, while avoiding lower-risk patients from the potential side effects or ineffectiveness of treatments. Furthermore, it may also reduce overall associated costs. It is not uncommon that interventions in clinical practice are usually aimed at high risk or high cost patients who need to be managed carefully and proactively. There are no pharmacological treatments approved by the Food and Drug Administration (FDA) for patients with MCI;^{6,15} however, results of randomized clinical trials (RCTs)¹⁶ and meta-analysis studies¹⁷⁻²¹ showed modest benefits of cholinesterase inhibitors²² (ChEIs: donepezil, galantamine and rivastigmine) on delaying the progression from MCI to AD.

In Paper 1, we examined the predictive ability of multi-biomarker score, computed from baseline cerebrospinal fluid (CSF) biomarker levels, to stratify MCI patients according to their risk of progression from MCI to AD. The hazard ratio for MCI patients with a high-risk score (the 3rd, 4th, and 5th quintiles of the score) or an intermediate-risk score (the 2nd quintile) were about 4 (95% confidence interval [CI],

1.93-7.26) and 2 (95% CI, 0.86-4.35) times greater than MCI patients with a low-risk score (the 1st quintile), respectively. Although the effect size was non-significant when comparing the intermediate-risk group to the low-risk group, this was likely due to the small sample size of the study used in Paper 1. In this study, we examined the cost-effectiveness of stratified treatments, defined by the high-, intermediate-, and low- risk groups from Paper 1, on MCI patients. We compared the targeted treatments on MCI patients based on their risk levels of developing AD defined by the test results of CSF biomarkers to no biomarker testing where treatment was either initiated early on MCI patients or late when only MCI patients convert to AD.

3.2 Methods

In a cost-effectiveness analysis (CEA) framework, we developed a state-transition Markov model to estimate the costs and benefits of targeted treatment on MCI patients based on their risk levels of developing AD using test results of CSF biomarkers, and the effects of no test results involved. We used results from the primary data analysis and published literature to derive relevant parameters in our decision model. Costs and outcomes were discounted 3% annually per US recommendation.²³ We adopted the societal perspective (including formal and informal costs) and a lifetime horizon.

3.2.1 Model structure

Figure 3.1 illustrates the model structure that computed the effect of testing to stratify MCI patients into different risk levels of developing AD combined with or without pharmacological treatments compared with treatment strategies without test information by simulating a hypothetical cohort of 65-year-old patients with MCI through distinct health states defined by the presence of AD severity (mild, moderate, or severe as determined by the Clinical Dementia Rating scale) and residential settings (community or nursing home). In pre-specified time intervals of one year (the Markov cycle), patients could remain in the same health state, transition to another health state or die. MCI patients who developed AD would transition to mild AD living in a community setting. Each year patients with AD could progress in severity (i.e., from mild to moderate AD or from moderate to severe AD) or could transition to a nursing home. Furthermore, once AD patients entered a nursing home we assumed that they would remain in the institution until death regardless of their disease severity.²⁴ Because patients with severe AD are more likely to move from community to nursing home than patients with mild or moderate AD and the modest proportion of patients transition to nursing home in the mild or moderate AD stage based on the parameters used in our model..

3.2.2 Primary treatment strategies

We evaluated four treatment strategies for MCI patients. We considered two “test-treat” strategies for which CSF biomarker testing was conducted to categorize MCI patients into three risk groups (high, intermediate and low) of developing AD defined by CSF biomarker score in Paper 1,²⁷ and then stratified treatment was decided according to patients’ risk levels including treating only the high risk group or treating high or intermediate risk groups. We compared these two “test-treat” strategies to alternatives without test information, in which no MCI patients were treated (no MCI treatment) or all MCI patients were treated (MCI treatment). These four strategies are detailed as follows:

- 1) No MCI treatment: treat only if MCI patients convert to AD
- 2) Treat MCI patients with high-risk biomarker scores but treatment stops if patients convert to AD
- 3) Treat MCI patients with high- or intermediate- risk biomarker scores but treatment stops if patients convert to AD
- 4) MCI treatment: treat all MCI patients but treatment stops if patients convert to AD

The effects of treating MCI patients are to delay the progression from MCI to AD and thereby to reduce the associated costs in the AD stages (high utilization of healthcare resources). We assumed that if patients received treatment in the MCI stage, they would not be eligible for treatment when they convert to AD based on expert opinion, but evaluated this assumption in a sensitivity analysis. Similarly, the effects of treating AD patients was to delay the progression to more severe dementia stages and indirectly reduce the probability of nursing home placement because the transition from community to nursing home is conditional on the disease severity.

3.2.3 Parameter sources

We used results from the primary data analysis using data of the Alzheimer's Disease Neuroimaging Initiative (ADNI-1),²⁸ published literature, and meta-analyses²⁰ to derive the predictive risks for progression from MCI to AD, mild to moderate AD, and moderate to severe AD, and the estimates of the impact of treatments on disease progression in the MCI and AD stages. **Table 3.1** summarizes the parameter estimates and their 95% confidence intervals (CIs). Furthermore, we characterized the quality of studies from which input parameters were derived (**Appendix 3.A**),²⁹ the quality of studies, evaluated based on three dimensions: study design, internal validity, and external validity, are good in the aspect of study design, fair in the internal validity (4 out of 23 studies are low or poor), and low quality in the external validity, respectively.

3.2.3.1 Disease progression

We assumed all transitions occur in the middle of each year, with transitions from MCI to the mild AD stage occurring first, followed by transitions from mild to moderate or severe AD. Death can occur from any health state and individuals could only experience one transition in a year (model cycle), such as from MCI to mild AD, mild to moderate AD, or moderate to severe AD.²⁵

We estimated the annual transition probabilities from MCI to AD contingent on the risk groups (high, intermediate, and low) defined by CSF biomarker scores using 6-year follow-up data from the ADNI (Paper 1). In brief, we summarized baseline CSF biomarker levels into a multi-biomarker score²⁷ and defined three risk groups: high risk (defined by the 3rd, 4th, and 5th quintiles of the multi-biomarker score), 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 function. For each risk group, we converted the 6-year cumulative probability into an annual

probability of developing AD and used this annual probability in our decision model and assumed it to be constant over time.

For transitions among AD stages, we used more recent/updated probabilities estimated by Spackman et al. using data from the Uniform Data Set (UDS) of the National Alzheimer Coordinating Center (NACC),²⁴ which includes patients receiving contemporary AD care. Spackman et al. provided estimates of the stage-to-stage transitions and community to nursing home transitions conditional on AD stage separately. We computed the combined stage and nursing home transition probabilities (e.g., moving from mild AD residing in a community setting to moderate AD residing in a nursing home) by multiplying stage-to-stage and community-to-nursing home transitions for each possible combination of disease severity and residential setting (**Table 3.1 & Appendix 3.B**). In Spackman's study, disease stage-to-stage transitions were assumed to occur independently of setting, whereas nursing home transitions were conditional on the disease severity.^{24,30}

3.2.3.2 Treatment effectiveness

We derived estimates of treatment efficacy of ChEIs separately for MCI patients and AD patients. The effectiveness of treatment was modeled as the reduction of the annual transition probability by a percentage, defined by a relative risk (RR). For MCI patients, we multiplied the transition probabilities of developing AD by the RR to estimate the potential impact of treatment on delaying the progression from MCI to AD. Similarly, the effectiveness of treatment for AD patients was measured by the reduction of the following transition probabilities by a percentage: from mild to moderate AD, mild to severe AD, and moderate to severe AD. We further assumed that, given an AD severity stage, that treatment had no effect on the transitions from community to nursing home.

However, because treatment affected the progression through the AD severity stages, there was an overall reduction in nursing home placement among the treated patients.

The effectiveness of treating MCI patients with ChEIs was derived from a recent Cochrane review²⁰ (the comparison with other systematic reviews of ChEIs on MCI patients is shown in **Appendix 3.C**). That review reported an effectiveness of ChEI treatment for MCI patients of 0.69 (95% CI, 0.47-1), 0.67 (95% CI, 0.55-0.83) and 0.84 (95% CI, 0.7-1.02) for years one, two and three, respectively. We used the 3-year effect of 0.84, which presented 16% risk reduction on the progression from MCI to AD and assumed that this persisted for only three years of treatment.

The effectiveness parameter of ChEI treatment was 0.58 (95% CI, 0.35-0.76) and 0.95 (95% CI, 0.64-1.41) for patients with mild AD or moderate AD, respectively. The RR applied to patients with moderate AD was derived directly from an RCT,³⁵ whereas we used the 0.8 (95% CI, 0.5-1.2) MMSE (mini-mental state examination) point increase over two years among AD patients with donepezil treatment from the same RCT to compute the treatment effectiveness (RR) for patients with mild AD. We simulated the trial cohort over two years and calculated the average MMSE (the clinically defined ranges for mild and moderate AD) for the treatment and control groups, and then derived the reduction in annual progression, measured as RR, from the mild to moderate stage that would yield a 2-year difference of 0.8 in the average MMSE scores while directly using the RR of 0.95 from the same RCT for the reduction in annual progression from the mild to severe, and the moderate to severe stages. The average MMSE score for the mild, moderate and severe stage was 24, 14, and 6, respectively. The trial cohort included 51% patients with mild AD and 49% patients with moderate AD, and the annual progression from the mild to moderate, the mild to severe, and the moderate to severe were 0.167, 0.014, and 0.299 (**Table 3.1**).

Owing to the limited evidence from clinical trials¹⁶ and meta-analysis studies,¹⁷⁻²¹ we assumed the treatment effect duration for MCI patients persisted for only 3 years. Conversely, the effect of ChEI treatment initiated for AD patients was assumed to continue until either they discontinued therapy due to adverse events or moved to the severe stage where the treatment was terminated. The reason we stopped treatment for severe AD patients was because our treatment parameters were derived from the largest clinical evidence base reviewed by Bond et al.,³⁶ and treatment is only approved by the FDA for mild or moderate AD patients. We did not consider the residual effect from treatments.

3.2.3.3 Adverse events (AEs) associated with treatment

The AEs associated with ChEI treatment included diarrhea, nausea, cramps, headache, and serious AEs as reported in prior RCTs.²⁰ The reported increase in the risk of AEs due to treatment between the treatment and the control groups for MCI and AD patients, which were 1.09 (95% CI, 1.02-1.16)²⁰ and 2.51 (95% CI, 2.14-2.95),³⁷ respectively. Also, the result from a systematic review³⁸ of the annual risk of AEs in the placebo arm of donepezil trials for MCI patients was used as the baseline risk (0.23). The annual risk of AEs associated with treatment was computed as $0.23 \times 1.09 = 0.25$ and $0.23 \times 2.51 = 0.58$ for MCI and AD patients, respectively. Among MCI or AD patients with treatments, 25% or 58% of them would experience treatment-induced AEs compared to 23% for those who had no treatment, respectively. We applied the risk difference between the treatment and the control groups ($0.25 - 0.23 = 0.02$ and $0.58 - 0.23 = 0.35$ for MCI and AD patients, respectively) in the model, which means that we only allowed treated patients to experience an AE. Once the treatment terminated, no AE event occurred in the model.

3.2.3.4 Adherence

Results from a systematic review³⁷ 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%) with the study period of 6 months for all but two studies. We derived the withdrawal rate due to treatment-induced AEs as the difference in withdrawal rates between the treatment and the control groups, which was about 10% (95% CI, 7-13%) per 6-month span. Furthermore, we extrapolated the 6-month rate into an annual rate and derived an annual withdrawal probability of 19% (95% CI, 14-24%) conditional on experiencing an AE. We applied this annual probability derived from AD patients to MCI patents. We also calculated the annual probability of withdrawal from treatment due to other reasons (excluding AEs) as 4.9% (95% CI, 3.7%-6.3%) and applied this probability to both MCI and AD patients receiving treatment.

3.2.3.5 Health utilities

Our health outcome measure is quality-adjusted life years (QALYs), as recommended by the Panel on Cost-Effectiveness in Health and Medicine.³⁹ QALYs are a composite measure of survival (longevity) and quality of life, where survival time is weighed by individuals' health-related quality of life, as measured by health utilities.⁴⁰ Individuals in perfect health are assigned a health utility value of 1, with lower values representing worse quality of life and a value of 0 representing dead.

We assigned utilities by disease severity and residential settings based on analyses by Neumann et al,^{31,41} because it was one of the few studies that estimated health utilities for joint states defined by disease severity and residential settings. Due to the absence of range of utilities by residential settings reported in their study, we applied the estimates of the SD for AD patients dwelling in the community to AD patients in the nursing home. In addition, we also accounted for the disutility resulted from the AEs due

to the treatment. We used the point estimate from other studies, such as the AEs due to aspirin,⁴³ because the majority of AEs reported in the clinical trials were mild.^{20,37}

3.2.3.6 *Excess mortality*

The annual excess mortality rate among patients with severe AD was estimated at 0.11 by the additive model.^{44,45} We assumed that patients with moderate AD would experience half of the excess rate (i.e., we added $0.11/2$ to the background death rates for patients with moderate AD). We assumed that this additive effect is the same regardless of the patients' age or gender.⁴⁴ Accordingly, the mortality risk in each disease stage for AD patients was estimated by combining the age-specific, all-cause mortality rates⁴⁶ with an additive effect of 0.055 for patients with moderate AD and 0.11 for patients with severe AD. We assumed that the mortality rate for MCI patients and patients with mild AD are equal to the background all-cause mortality rate.

3.2.3.7 *Cost*

All cost estimates were inflated to 2013 US dollars with the use of the consumer price index (CPI)⁴⁷ if needed. Moreover, in order to be able to apply the cost estimated from European countries if any, costs in the local currency were converted to the corresponding US dollars using the gross domestic price purchasing power parity (GDP-PPP) conversion rates⁴⁸ and further inflated to the 2013 US dollars using the CPI.

3.2.3.7.1 *Formal and informal care*

While many studies to date have assessed the economic burden of dementia (including AD and other type dementia),⁴⁹⁻⁵³ few report costs by disease severity together with residential settings, as needed for our model. In the US setting, only Rice et al.⁵⁴ and Leon et al.⁵⁵ reported AD costs by these two attributes, however, they were published

almost twenty years ago so that may not represent current practice. The most recent studies were conducted outside the US,^{56,57} which would not be pertinent to our analysis due to differences in healthcare systems and culture. Moreover, few recent meta-analyses^{49,52,53} comparing cost-of-AD studies (categorized by disease severity or residential settings, or both) were available, however, the studies conducted in the US were done before 2000,⁵⁸⁻⁶⁰ and their cost estimates were in the range of our cost parameters, or no cost information applicable to our study.⁶¹⁻⁶⁴ Accordingly, we used the cost estimates as reported by Leon et al.,⁵⁵ which included data from 9 states with a larger sample size (n=674).

In the Leon study, summaries for community-based dwelling, institutionalization (assisted living and nursing home), formal (defined as paid health services) and informal care (defined as unpaid care provided by a primary family caregiver) and costs by disease severity were reported separately. The cost of informal caregiving was measured by the amount of time spending on the aspect of activities of daily living (ADL) and instrumental activities of daily living (IADL). Hours of care were multiplied by national hourly wage rates for ADL and IADL, respectively. We converted monthly costs from the study to annual costs and assigned them to the comparable health states in our model. Due to the lack of the variance (95% CI) of costs reported in the study, we further assumed that the cost estimate for each health state in the model was 50% lower or higher from the mean of point estimates as the lower bound and the upper bound, respectively.

For the costs incurred in the MCI stage, we used data from Luppia et al.⁶⁵ to inform direct costs, including medical cost, pharmaceuticals, and non-medical costs (home care, assisted living, and transport), for patients with MCI, albeit it was not significantly higher when compared with patients without cognitive deficit.

We didn't account for the indirect costs resulting from the loss of productivity of patients due to the advanced age. The CEA results presented included both formal and informal costs unless specified.

3.2.3.7.2 Medication

We based the unit costs for AD medications on the average wholesale price reported in the Red Book.⁶⁶ The daily costs for these drugs were estimated based on their recommended dose and usage from the licensed labels. We estimated the medication cost at the lowest available market price (\$7.79) per day (the cost for donepezil 5mg is the same as 10mg) and largest pack size. We estimated the annual drug costs as $365.25 \times 7.79 = \$2,845$. For the follow-up cost due to the treatment, we continued the assumption made by previous study³¹ that donepezil would induce two and one extra office visits every year along with the treatment effect duration for MCI and AD patients, respectively. The one office visit was associated with \$81 as estimated by the previous study.³¹

3.2.3.7.3 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 & Medicaid Services hospital outpatient fee schedule as reported in the previous study.⁶⁷

3.2.4 Analysis

3.2.4.1 Base-case analysis

We calculated expected discounted lifetime costs and discounted QALYs for each of the four strategies. Cost-effectiveness results were presented as the incremental cost-

effectiveness ratios (ICERs), measured as the additional cost for per additional QALY gained ($\Delta c/\Delta e$)⁴⁰ by the following steps:

- 1) We ranked strategies by increasing total cost and eliminated strongly dominated strategies. A strategy is strongly dominated if it is more costly but less effective than another strategy.
- 2) We calculated the ICER for each non-dominated strategy compared to the next most expensive non-dominated strategy.
- 3) We identified and eliminated all weakly dominated strategies. A strategy is weakly dominated if it has a higher ICER than a more costly strategy, indicating that the strategy is more costly and less effective than a combination of other strategies.
- 4) ICERs are recalculated after removal of a weakly dominated strategy. This process may need to be iterated when there are several weakly dominated strategies.
- 5) We compared the remaining ICERs with a willingness to pay (WTP) threshold for a QALY, which we varied from \$50,000 to \$100,000 per QALY. The strategy with the highest ICER that is lower than the designated WTP is the most cost-effective strategy.

3.2.4.2 Sensitivity analysis

In addition to the base-case analysis, we conducted deterministic (using discrete alternative values in the simulation) and probabilistic sensitivity analyses, where all input parameters are simultaneously varied by sampling from probability distributions for each parameter, to evaluate uncertainty with respect to the parameter assumptions. The specific description of how we derived the value or range of each input parameters is

presented in the above section of 3.2.3 and the characteristics of each parameter are shown in **Table 3.1**.

3.2.4.2.1 Deterministic sensitivity analysis

In the deterministic sensitivity analysis (DSA), we varied one parameter at a time (one-way) or two parameters simultaneously (two-way) to recalculate lifetime costs and QALYs for each treatment strategy, and then determine which parameter is more influential to the CEA results, defined as the widest range of recalculated ICERs and also crossing a decision threshold. We drew upper and lower bound values of each parameter from published 95% CI estimates or used 50% value lower or higher to the mean if not available.

3.2.4.2.2 Probabilistic sensitivity analysis

We conducted the probabilistic sensitivity analysis (PSA) using second-order Monte Carlo repeat sampling methods⁶⁸ in which values of all input parameters were randomly drawn from the distributions simultaneously to account for the parameter uncertainty. We used beta distributions to represent uncertainty in the probability and utility parameters because such estimates are constrained on the interval [0, 1]. We characterized uncertainty in RR estimates using the log-normal distribution and we used gamma distributions to reflect uncertainty in costs, which have a lower bound at 0 and are generally right-skewed.⁶⁹ **Table 3.1** presents probabilistic input parameters and their corresponding distributions. Uncertainty around these parameters was considered simultaneously and the parameters were entered into the model as pre-specified, independent distributions except health utilities. To ensure only meaningful scenarios, we required that the rank order of QALY weights (i.e., utilities) in each PSA iteration was aligned with disease severity and residential settings,⁴² which implied that the health

utility of $u(\text{MCI}) > u(\text{mild AD}) > u(\text{moderate AD}) > u(\text{severe AD})$ and $u(\text{community}) > u(\text{nursing home})$. In this model, we applied the preference ordering algorithm developed by Goldhaber-Fiebert and Jalal⁷⁰ to ensure the health utility drawn in the PSA was presented in the preferred order by the disease severity and the residential settings.

Fixed input parameters included the treatment effect duration for MCI patients (fixed at a 3-year interval), the excess mortality rate due to AD, and discount rates of costs and health outcomes. We conducted 10,000 PSA iterations. We presented the PSA results using the cost-effectiveness acceptability curve (CEAC),⁷¹ which depicts the percentage of times that a strategy is cost-effective in the PSA iterations at different WTP thresholds.

The PSA simulation result was also used to present the result of the base-case analysis as the means of discounted life time costs and QALYs for each strategy to account for the nonlinear feature of Markov model used in the current study, in which the input parameters should ideally be modeled with probability distributions instead of point estimates (the mean) because the a model outcome, $f(x)$, is a nonlinear function of input parameters, x , so that the expected value of $f(x)$ is not equal to the function of the expected value of x (point estimate).^{68,72}

3.2.4.3 Scenario analysis

We constructed treatment scenario analyses by varying treatment assumptions in the MCI and AD stages. In a best-case scenario, we applied the assumption that the patients would receive treatment when they convert to AD regardless of their treatment status in the MCI stage to the four primary treatment strategies. Next, we considered the treatment scenario conditional on the disease course of AD (MCI, AD or both), assuming: 1) all patients would be treated in both MCI and AD stages (treat both), and we varied the effectiveness of treatment at the AD stage among those patients who were

also treated in the MCI stage, 2) treat all MCI patients but treatment stops if patients convert to AD (treat MCI only), and 3) treat only when MCI patients convert to AD (treat AD only). Finally, we considered a scenario no treatment was initiated in either the MCI or AD stage (treat neither).

All analyses were performed in TreeAge (version TreeAge Pro 2013, TreeAge Software, INC, Williamstown, Mass), and Microsoft Excel (Microsoft Corp., Redmond, WA).

3.3 Results

3.3.1.1 AD-free life time

The AD-free life time provides a measure of the average duration of time patients spend without AD under the different strategies. We found that AD-free life years associated with no MCI treatment was 3.60 years. Treating MCI patients at the high-risk level, treating only those at the high- or intermediate-risk level, or treating all MCI patients produced an extra 1.6, 2.3, and 3.3 AD-free life months compared to no MCI treatment. Specifically, **Figure 3.2** displays the AD-free months gained by MCI treatment compared with no MCI treatment (95% credible interval: 0.77-5.74).

3.3.1.2 Base-case analysis

As shown in **Table 3.2**, the base-case results indicated that the two test-treat strategies were less costly and less effective than the other two strategies with no testing. Moreover, treating MCI patients at high risk was weakly dominated because it had a higher ICER than the MCI treatment strategy. No MCI treatment resulted in the highest cost and the highest effectiveness (QALYs), with an ICER of \$29,400 per QALY compared with MCI treatment. The increased cost associated with no MCI treatment is because patients with AD are associated with high healthcare use; the increased effectiveness resulted from the better treatment effectiveness for patients with mild AD than for MCI patients.

We decomposed the total discounted lifetime costs and total discounted QALYs generated by each strategy by disease severity and residential settings. The cost accumulated in each disease stage/residential setting was increased with the weighted time (QALYs) spent in that state (health utility stands for the weight for each health state defined by the disease severity and residential setting). MCI treatment was associated with the greatest AD-free life years gained but with a shorter discounted quality-adjusted

time spent in the mild AD/community state, whereas no MCI treatment exhibited the longest time in the mild AD/community state (**Appendix 3.D & 3.E**).

3.3.2 Sensitivity analysis

3.3.2.1 Deterministic sensitivity analysis

Because the two strategies with testing information (treat high, and treat high or intermediate) were not cost-effective in any scenario where all possible values of point estimates for parameters were applied, we presented the results of DSA by simply comparing MCI treatment and no MCI treatment strategies.

3.3.2.1.1 One-way DSA

The tornado diagram (**Figure 3.3**) showed that the CEA result was sensitive to treatment effectiveness for patients with mild AD, treatment effectiveness for MCI patients, health utility for patients with mild AD living in the community, informal and formal costs in the mild AD/community state, and the annual risk of transition to nursing home for patients with mild AD. We further searched for the threshold of a parameter that a preferred strategy would switch from no MCI treatment to MCI treatment at WTP of \$50,000/QALY. Specifically, MCI treatment became cost-effective when the RR of treatment effectiveness for MCI patients was less than 0.77 (base-case value, 0.84) (**Appendix 3.F**), the RR of treatment effectiveness for patients with mild AD was greater than 0.66 (base case value, 0.58) (**Appendix 3.G**), the excess mortality rate due to severe AD was less than 0.27 (base-case value, 0.11) (**Appendix 3.H**), and the overall annual risk of progression from MCI to AD reduced 50% (**Appendix 3.I**), in which the probability for MCI patients at high risk decreased from 0.244 to 0.122, for patients at intermediate decreased from 0.108 to 0.054, and for MCI patients at low risk decreased from 0.065 to 0.033. We did not find a threshold value when we varied the duration of

treatment effect on MCI patients (up to 10 years) (**Appendix 3.J**), the annual cost of medication (down to \$100 per year) (**Appendix 3.K**) or varied the time horizon of the analysis (range, 10-35 years) (**Appendix 3.L**).

3.3.2.1.2 Two-way DSA

In addition to varying one parameter at a time, we conducted two-way DSA by varying 1) treatment effectiveness for MCI patients vs. treatment effectiveness for patients with mild AD, and 2) the duration of the treatment effect on MCI patients vs. treatment effectiveness for patients with mild AD. Results in **Appendix 3.M** shows the combinations of these parameters for which MCI treatment is cost-effective at WTP of \$50,000/QALY. On the other hand, in order for no MCI treatment to remain as the optimal strategy, the RR of treatment effectiveness for patients with mild AD would need to ≤ 0.6 if MCI patients have received treatment for 6 years (**Appendix 3.N**).

3.3.2.2 Probabilistic sensitivity analysis

Figure 3.4 presents the probability that each strategy is cost-effective for varying values of WTP (i.e., the CEAC). Specifically, no MCI treatment was cost-effective with 63% of time in the PSA simulation (10,000 iterations) over 37% of time for the MCI treatment strategy at WTP of \$50,000/QALY. Given the current evidence, however, the treat high risk and treat high or intermediate risk strategies have shown relative low chances to be cost-effective compared with strategies of MCI treatment and no MCI treatment. They had a limited chance to be cost-effective when WTP is higher than \$30,000/QALY. Moreover, in addition to the probability of being the cost-effective strategy, the incremental cost-effectiveness plane illustrated the considerable variation of the simulated results based on 10,000 iterations. Here, we presented the joint distribution of incremental costs and QALYs between no MCI treatment and MCI treatment strategies

(Appendix 3.O).

3.3.3 Scenario analysis

3.3.3.1 The best-case scenario

In addition to the base-case analyses where we assumed that if MCI patients have received treatment, they would not be treated when they convert to AD, **Table 3.3** presents the CEA results of all treatment strategies assuming that treatment would be allowed when patients convert to AD regardless of their treatment status in the MCI stage. As expected, the QALYs increased with the increasing number of treated MCI patients and the strategy of treating all patients both in MCI and AD stages (MCI treatment) was associated with the highest cost and highest QALYs, with an ICER of \$28,100 per QALY. The CEAC showed that the probability that MCI treatment is cost-effective is 77% at a WTP of \$50,000/QALY (**Appendix 3.P**). A one-way sensitivity analysis of this scenario showed that treating only when MCI patients convert to AD (no MCI treatment) would be cost-effective over the other three strategies if the RR of the treatment effectiveness for MCI patients were greater than 0.91 (base-case value, 0.84) (**Appendix 3.Q**). While varying the treatment effectiveness for patients with mild AD in the strategy of treating all patients both in the MCI and AD stages but holding it at the base-case value (RR=0.58) in the other three strategies, the strategy of no MCI treatment was cost-effective when the RR of the treatment effectiveness for patients with mild AD, which was changed only in the strategy of treating all patients both in the MCI and AD stages, was greater than 0.66 (**Appendix 3.R**).

3.3.3.2 Comparison of treatment scenarios

Next, we considered the treatment scenario conditional on the disease course of AD (MCI, AD or both). Without considering the test-treat strategies, we compared treat MCI

only and treat AD only to the treat both and treat neither scenario. **Table 3.4** shows that scenarios with treatment produced more QALYs and costs compared to no treatment. Among those scenarios with treatment, treat AD only produced more QALYs but also cost more than treat MCI only, and treat both was the scenario with the highest QALYs and costs with an ICER of \$28,700/QALY.

Table 3.4 also shows a trade-off among MCI, mild AD, and severe AD stages occurred between treat MCI only (MCI treatment) and treat AD only (no MCI treatment) scenarios with regard to QALYs gained by the disease severity. We found that patients would spend more weighted time (QALYs) in the MCI and the severe AD stage if they received the treatment in the MCI stage, whereas the amount of weighted time spent in the severe AD stage was reduced if they received treatment only if they convert to AD. Furthermore, treatment initiated in both MCI and AD stages produced more QALYs in the MCI stage but less QALYs in the moderate AD stage compared to the other strategies.

Our base-case results implied the net benefits of treating MCI patients with high-risk scores (the difference between treating only when MCI patients convert to AD [no MCI treatment] and treating MCI patients at high risk) and treating MCI patients with intermediate-risk scores (the difference between treating MCI patients at high or intermediate risk and treating MCI patients at high risk) produced fewer QALYs and was less costly; however, the net benefit of treating MCI patients with low-risk scores (the difference between treating all MCI patients [MCI treatment] and treating MCI patients at high or intermediate risk) generated more QALYs and was more costly. Due to this finding, it may be beneficial to target treatments on MCI patients with low-risk scores as priority. In this post-hoc analysis, we examined the scenario of treating MCI patients at low risk of developing AD, including two additional strategies - treat MCI patients with low-risk score and treat MCI patients with low- or intermediate-risk score. CEA results

showed treating MCI patients at low risk was cost-effective with an ICER of \$39,500 in this case (**Appendix 3.S**). **Appendix 3.T** shows the results for which treatment strategy would be cost-effective at WTP of \$50,000/QALY by varying parameters of treatment effectiveness for patients with mild AD and treatment effectiveness for MCI patients simultaneously. No MCI treatment and MCI treatment were more likely to be cost-effective compared to strategies of treat low and treat low or intermediate with a greater region of being preferable. Similarly, PSA results based on this scenario showed that no MCI treatment strategy was associated with 37% probability of being optimal at WTP of \$50,000/QALY, whereas it was 30% and 21% for treating all MCI patients and treating MCI patients at low risk, respectively. Strategies of no MCI treatment and treat low were intersecting at WTP of \$80,000/QALY (**Appendix 3.U**). **Appendix 3.V** presents the CEA results based on the assumption that patients would be treated regardless of their treatment status in the MCI stage. Similar to the primary treatment strategies, treat all patients both in the MCI and AD stages (MCI treatment) was cost-effective with an ICER of \$28,100/QALY.

3.4 Discussion

In this study, we aimed to assess the costs and benefits of the use of CSF biomarker testing to target treatments for MCI patients to delay the progression of AD compared with no testing where treatment was either initiated on all MCI patients or only when MCI patients convert to AD. We did not find that CSF biomarker testing added value to guide the decision whether or not to target treatments for MCI patients at higher risk in the primary analysis. While the biomarker results did allow us to distinguish high-risk patients from those at lower risk in Paper 1, there was no added benefit from stratified treatments for MCI patients at higher risk. This might be because we did not find satisfactory evidence of risk estimates on disease progression from MCI to AD by CSF biomarker scores in Paper 1. This could have been due to the study sample included in Paper 1, which included a high proportion of MCI subjects who were close to transitioning to AD.^{28,73} Also, neither the baseline biomarker scores at the time that cognitively normal controls had developed MCI nor the natural history of disease among MCI subjects was available for the adjustment of risk estimates. Thus, our CEA results may be most relevant for populations who are more proximal in time to the clinical diagnosis of AD. Moreover, we took a conservative perspective on the assumption of the treatment effectiveness for MCI patients due to the modest results from published studies.²⁰ This resulted in reduced benefit for targeting MCI patients based on their risk levels of developing AD compared with treating only when they convert to AD and consequently decreased the chance of being preferred for those strategies that targeted patients based on their risk levels. However, it is likely that MCI subjects enrolled in clinical trials that examined the treatment efficacy of ChEIs were heterogeneous and thus resulted in indefinite outcomes.⁶ With increasing refinement of diagnostic tools, our results may present different findings showing the potential value of biomarker testing.

On the other hand, CSF biomarker testing may be of value if treating MCI patients at low risk rather than those at high risk, as shown in our post-hoc analysis. CEA results in this scenario indicated that treating MCI patients with low-risk biomarker scores was cost-effective. In contrast, PSA results showed that treat low strategy was associated with lower chance of being preferable compared with strategies of MCI treatment and no MCI treatment. Strategies of treat low and no MCI treatment were intersecting at WTP of \$80,000/QALY. It seems that treating patients at low risk may be beneficial, although it is counterintuitive that interventions in clinical practice are usually aiming for high-risk or high-cost patients. It is possible that MCI patients at high risk are close to be clinically diagnosed of AD and the treatment with higher effectiveness would be forgone when they convert to AD if they received treatment (with lower effectiveness) in the MCI stage based on the model assumption. Accordingly, for the strategy of targeting MCI patients at higher risk, less benefit was generated due to the treatment in the MCI stage and no benefit was obtained in the AD stage.

Our decision model also focused on exploring the timing of pharmaceutical intervention MCI stage (MCI treatment) vs. AD stage (No MCI treatment) as this study was designed to investigate the potential of targeting treatments on MCI patients who are at risk of developing AD. Our results indicated that treating only when MCI patients convert to AD (no MCI treatment) was cost-effective compared to treating them upfront before AD (MCI treatment). The benefit of MCI treatment, conferred by way of a reduced progression to AD among patients with MCI only in the first 3 years, translated into an average gain of 3.3 months of AD-free time per patient. Compared with the treatment efficacy assumption made for patients with mild AD, this effect was smaller and lasted for a shorter period of time, which in turn resulted in the smaller expected benefit gained for the MCI treatment strategy. This finding was corroborated in the one-way and two-way DSAs showing a trade-off between treatment effectiveness for MCI patients and

treatment effectiveness for patients with mild AD. The strategy of MCI treatment is more likely to be cost-effective when the RR of the treatment effectiveness for patients with mild AD is greater than 0.66 and no MCI treatment had a bigger region of being preferable than MCI treatment in the two-way DSA. Moreover, our PSA results presenting by the CEAC and the incremental cost-effectiveness plane suggested approximate 63% and 37% of chance that no MCI treatment and MCI treatment strategies would be cost-effective at WTP of \$50,000/QALY, respectively, and considerable uncertainty exists.

Although current clinical practice (i.e., treating only when MCI patients convert to AD) was preferred based on our CEA results, the assumption adopted in this model that patients received treatments either in the MCI stage or AD stage but not both resulted in reduced benefits. Corroborating with scenario analyses that treatment initiated in both MCI and AD stages would produce the greatest benefits, this implied that alternative treatments for patients with mild AD with the RR not greater than 0.66 and comparable to the current treatment on MCI patients, which allows for the continued treatments, would have the significant impact on the CEA results. Accordingly, it is of value to investigate the feasibility of treatment continuum from MCI to AD stages

Many CEAs have assumed the cost offsets by treatment-induced delay of nursing home admission to reach cost-effectiveness; however, these cost offsets will be less substantial if differences in total AD costs (formal and informal) between residential settings was minimal from a societal perspective. A German study indicated that community-based dementia care is cost saving from the payer perspective due to substantially lower long-term care expenditures because of substituted unpaid caregiving (informal cost).⁷⁵ In the case of transitions from the community to a nursing home, informal care is replaced by formal care.⁷⁶ Thus economic expenditures for healthcare systems are more evident in an institutionalized setting, whereas informal

costs in a community-based setting place a greater economic burden on families.⁵³ Given that, the cost difference between residential settings contingent on the disease severity may be attributable only to whether the informal cost, especially in the community setting, was accounted for or not. In fact, studies have shown the small cost difference on AD patients between residential settings was found.⁵⁴ With the inclusion of informal costs, which was estimated by replacing informal caregiving activities with formal care (the replacement cost approach), in the CEA and no MCI treatment resulted in the greater amount of AD patients staying in the mild or moderate stages than MCI treatment in our case, it would not be feasible for MCI treatment to reach cost-effectiveness by means of costs offset by delaying nursing home admission.

Healthcare costs by disease severity of AD were the key parameter in our model. In order to assess the cost-effectiveness of different treatment alternatives, there is a need for reliable and updated data on costs and health utilities for different levels disease severity and residential settings. However, no recent cost data of disease severity by residential settings is available in the US setting, which may hamper the evaluation of treatment strategies conducted in our model. Furthermore, the estimates of costs varied from study to study^{49-53,77}, such as different measures used for disease severity, perspectives (societal, payers, or patients), included cost categories, as well as variability in care and support systems between countries.⁴⁹ It is also difficult to retrieve the cost estimates by disease severity, residential settings, and the cost category (outpatients, inpatients, pharmaceuticals and non-medical, etc.) simultaneously simply from one study. Due to the unavailability of recent data, we used the cost estimates, which were conducted about twenty years ago,⁵⁵ with the adjustment by inflation using the CPI. We further expanded the cost estimates into broad ranges in the sensitivity analysis and we found the findings were robust. Further studies focus on the cost estimates including community-based care with formal and informal service would enrich

the current results.

We acknowledge several limitations in the study. First, the cost information⁵⁵ applied in this study may be outdated due to the unavailability/inapplicability of recent data. Changes in many social and cultural factors are very likely to influence the model results. With the exercise of sensitivity analyses, however, we believe that our finding is still justifiable. Second, we did not incorporate all possible sources of uncertainty. For instance, patients' response to the pharmacological interventions was assumed to be consistent across different risk levels of progression from MCI to AD or among AD stages and also across the treatment duration. We also assumed that there is no residual treatment effect after treatment stops. Third, no recent treatment efficacy result on MCI patients is presented as the measure of the relative risk, which was used to estimate the treatment-associated reduction on the risk of progression to AD from MCI in our model (equals to multiply the RR with the transition probability). Most studies^{20,78,79} reported this parameter as the effect as the point difference of cognitive tests between the treatment arm and the control arm, such as MMSE or the AD and associated disorders (ADAS), instead of the risk reduction on transition to severer stages of AD (presented as the RR). Better than nothing, we applied the information of the point difference to indirectly derive the RR of progression from the mild to moderate AD stage for the treatment group versus the control group. Finally, the approach in the current study is definitely not comparable to decision models that were structured differently, such as using the apolipoprotein genetic testing combined with hypothetical treatments to decide the cost-effectiveness of the optimal treatment strategy on patients with MCI.³³

3.5 Conclusion

Still, decisions must be made, and in the absence of better evidence, appealing to published sources was a reasonable approach.⁸⁰ Based on the current evidence, this study illustrates the potential for early targeted interventions for MCI patients who are at risk of developing AD, especially for those at low risk. Moreover, Our model and the findings from our analyses could be used to guide further research evaluating the cost-effectiveness of other biomarkers used to target MCI treatment on MCI patients at increased risk of developing dementia.

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Table 3.1 Parameter inputs for the state-transition Markov model.

Parameter	Mean	95% CI	Distribution	Source
Annual probability of progression from MCI to AD by CSF biomarker score				27
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)	
Annual transition probability^a				24,30
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)				44,45
Treatment effectiveness (RR)				
MCI patients	0.84	0.70-1.00	Lognormal(-0.17, 0.096)	20
AD patients)	35
mild to moderate	0.58	0.35-0.76	Lognormal(-0.55, 0.198)	
moderate to severe	0.95	0.64-1.41	Lognormal(-0.05, 0.114)	
Treatment harm				
Annual prob. of AE (control)	0.23	0.2-0.26	Beta(173.78, 581.77)	38
AEs in MCI (RR)	1.09	1.02-0.16	Lognormal(0.086, 0.02)	20
AEs in AD (RR)	2.51	2.14-2.95	Lognormal(0.92, 0.08)	37
Withdrawal due to AE ^b	0.19	0.14-0.24	Beta(41.67, 181.76)	37
Withdrawal due to non-AE	0.049	0.037-0.063	Beta(52.37, 1016.4)	Assumed
Health utility				
MCI	0.73	0.58-0.88	Beta(23.86, 8.82)	33,41
AD				
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 ^c	0.99	0.988-0.991	Beta(9800, 99)	Assumed, ⁴³

Table 3.1 Continued.

Parameter	Mean	95% CI	Distribution	Source
Cost (\$, per person-year)				
MCI	7,744	3,872-11,617	Gamma(15.36, 0.0020)	65
Formal ^d				55
Mild AD				
community	9,104	4,552-13,657	Gamma(15.36, 0.0017)	
nursing home	49,371	24,685-74,056	Gamma(15.37, 3.11)	
Moderate AD				
community	13,452	6,726-20,178	Gamma(15.36, 0.0011)	
nursing home	53,736	26,868-80,604	Gamma(15.37, 2.86)	
Severe AD				
community	20,276	10,138-30,414	Gamma(15.37, 7.58)	
nursing home	57,584	28,792-86,377	Gamma(15.37, 2.67)	
Informal ^e				55
Mild AD				
community	11,528	5,764-17,291	Gamma(15.36, 0.0013)	
nursing home	1,229	615-1,844	Gamma(15.32, 0.0125)	
Moderate AD				
community	19,955	9,978-29,933	Gamma(15.36, 7.70)	
nursing home	944	472-1,416	Gamma(15.34, 0.0163)	
Severe AD				
community	20,115	10,058-30,173	Gamma(15.37, 7.64)	
nursing home	998	499-1,497	Gamma(15.32, 0.0153)	
Drug (donepezil)	2,844	1,422-4,266	Gamma(15.35, 0.0054))	AWP, ⁶⁶
Office visit due to treatment (per time)	81	41-122	Gamma(14.88, 0.1837)	31
CSF biomarker testing (per person)	315	158-473	Gamma(15.50, 0.0492)	67

^aWe obtained the combined stage and nursing home transition probabilities by multiplying stage-to-stage and stage-to-nursing home transitions.

^bAnnual probability derived from 6-month data by the exponential function ($0.19=1-\exp[-0.1032*2]$).

^cIncorporated as disutility due to the treatment

^{d, e}Estimates from published studies.

Abbreviation: AD, Alzheimer's disease; MCI, mild cognitive impairment; RR, relative risk; AE, adverse event; AWP, average wholesale price; Com, community; NH, nursing home; CI, confidence interval.

Table 3.2 Base-case results (per patient) for CSF biomarker testing and treatment on patients with MCI.*

Strategy [§]	Cost (\$)	QALYs	ICER (\$/QALY) [¶]
Treat high or intermediate	265,211	7.487	-
Treat high	265,445	7.499	Weakly dominated
MCI treatment	265,665	7.515	16,500
No MCI treatment	270,609	7.683	29,400

*If MCI patients received treatment, no treatment was provided when they convert to AD.

[§]MCI treatment stands for treating all MCI patients but treatment stops when they convert to AD, treat high was treating MCI patients at high risk, treat high or intermediate was treating MCI patients at high risk or intermediate risk, and no MCI treatment was treating only when MCI patients convert to AD (based on clinical expert opinion).

[¶]The value was rounded to the nearest \$100.

Abbreviation: CSF, cerebrospinal fluid; MCI, mild cognitive impairment; AD, Alzheimer’s disease; ICER, incremental cost-effectiveness ratio.

Table 3.3 Cost-effectiveness results of allowing treatments in both MCI and AD stages (best-case scenario).*

Strategy [§]	Cost (\$)	QALYs	ICER (\$/QALY) [¶]
No MCI treatment	270,609	7.683	-
Treat high	272,662	7.748	Weakly dominated
Treat high or intermediate	274,012	7.793	Weakly dominated
MCI treatment	275,579	7.860	28,100

[§]MCI treatment stands for treating all MCI patients, treat high was treating MCI patients at high risk, treat high or intermediate was treating MCI patients at high risk or intermediate risk, and no MCI treatment was that treat only when MCI patients convert to AD (based on clinical expert opinion).

[¶]The value was rounded to the nearest \$100.

Abbreviation: MCI, mild cognitive impairment; AD, Alzheimer's disease; ICER, incremental cost-effectiveness ratio.

Table 3.4 ICERs and QALYs decomposition of treatment scenarios by disease severity.

Scenario*	Costs (\$)	QALYs	ICER (\$/QALY) [†]	QALYs decomposition			
				MCI	Mild AD	Moderate AD	Severe AD
Treat neither	259,357	7.292	-	3.602	2.181	0.715	0.794
MCI treatment	265,665	7.515	28,300	3.873	2.159	0.705	0.777
No MCI treatment	270,609	7.683	Weakly dominated	3.602	2.759	0.632	0.690
Treat both	275,579	7.860	28,700	3.873	2.670	0.631	0.685

*Treat neither: no treatment in the either MCI or AD stages; MCI treatment: treat all MCI patients but treatment stops when they convert to AD; No MCI treatment: treat patients only when they convert to AD; treat both: treat patients in both MCI and AD stages.

[†]The value was rounded to the nearest \$100.

Abbreviation: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; DOM, dominated; MCI, mild cognitive impairment; AD, Alzheimer's disease.

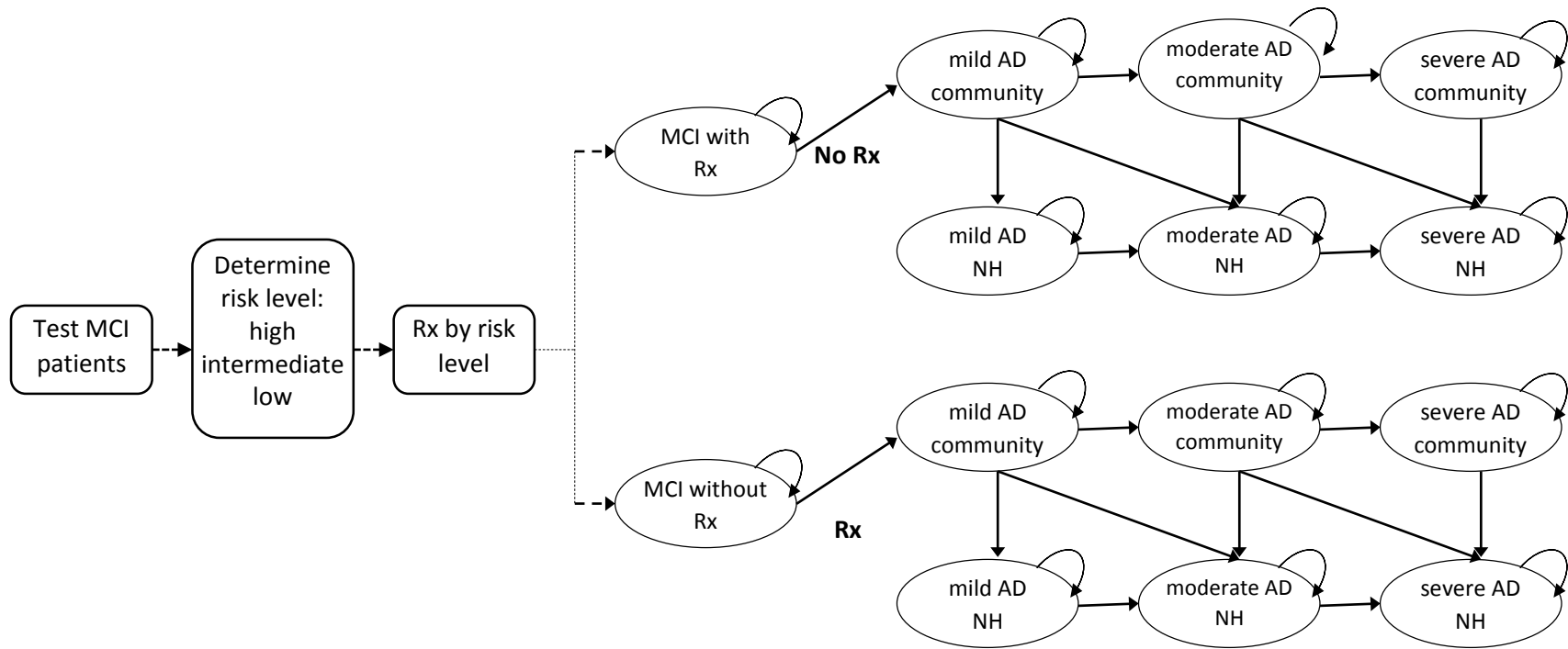


Figure 3.1 Schematic diagram of CSF biomarker testing and subsequent treatments on patients with MCI. CSF, cerebrospinal fluid; MCI, mild cognitive impairment; AD, Alzheimer's disease; Rx, treat; NH, nursing home.

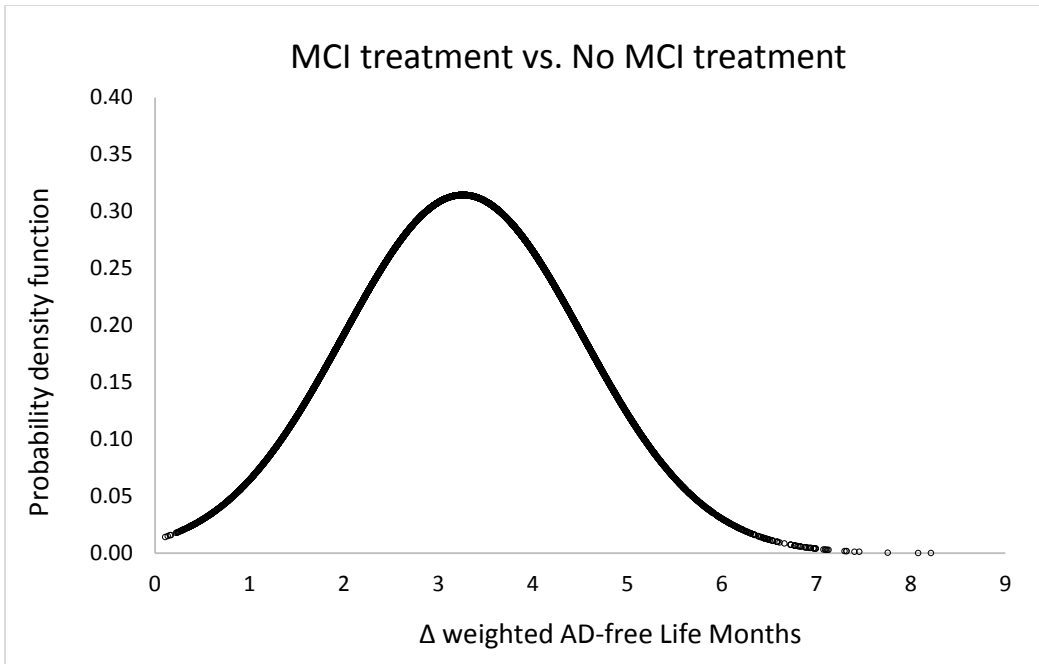


Figure 3.2 Distribution of the weighted (health utility) AD-free life months gained with MCI treatment compared to no MCI treatment based on PSA 10,000 iterations.

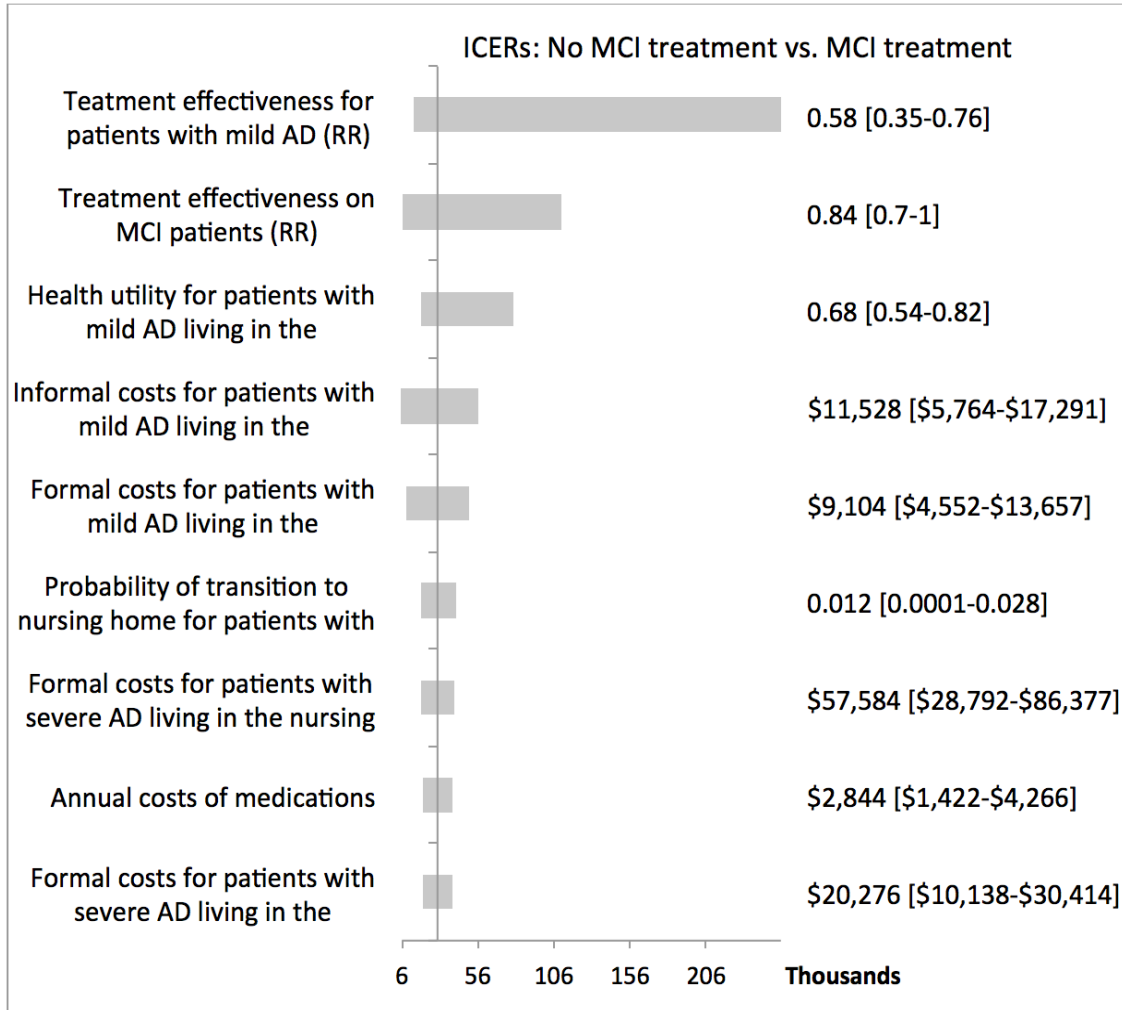


Figure 3.3 One-way sensitivity analysis tornado diagram. The variables were sorted by their importance. The longer bars indicate parameters are the most important parameters. AD, Alzheimer’s disease; MCI, mild cognitive impairment; ICERs, incremental cost-effectiveness ratios; RR, relative risk.

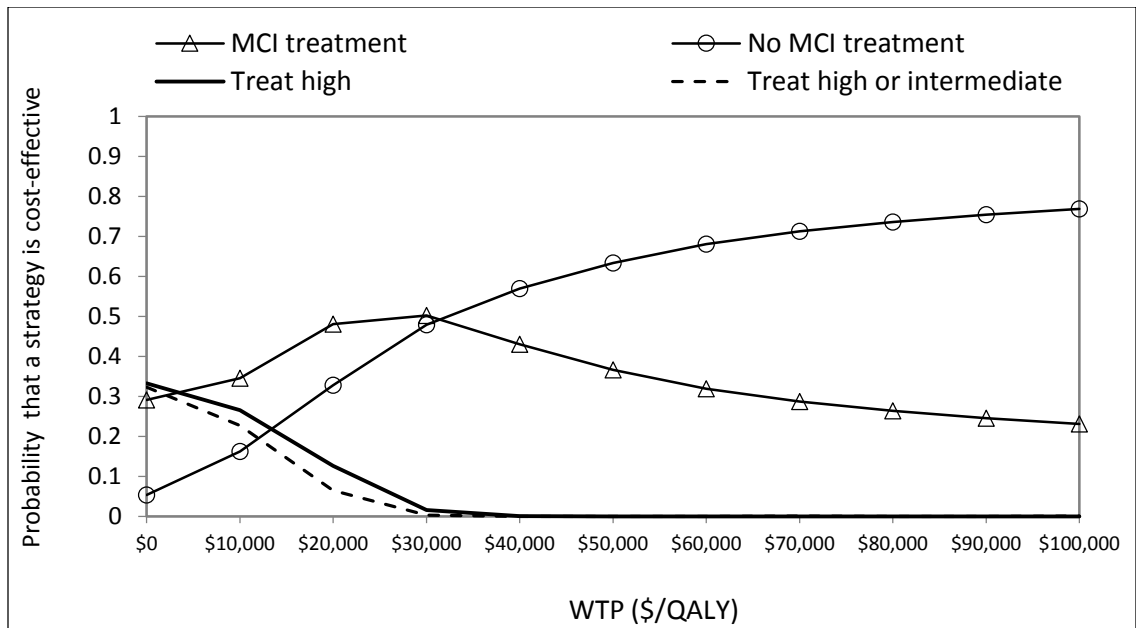


Figure 3.4 Cost-effectiveness acceptability curve showing the probability that each strategy is cost-effective at various willingness to pay (WTP) thresholds. QALYs: quality-adjusted life years; WTP: willingness to pay.

Appendix 3.A Evidence table of input parameters in the model, adapted from Braithwaite et al.' study.²⁹

Parameter	Data Source	Reference	Strength of evidence		
			Study design ^a	internal validity ^b	external validity ^c
Probability (annual)					
Mortality rate in absence of AD	Observational; life tables	46	1	good	low
Mortality rate attributable to AD	Observational (systematic review); 1 study in similar population	44	2-2	good	high
Risk of progression to AD from MCI by CSF biomarker levels	Observational (cohort); ADNI (N=195)	27	1	fair	low
Risk of disease progression among AD stage	Observational (NACC-UDS, CERAD); 2 study in similar population	24,30	1	fair	low
Probability of moving to nursing home conditional on disease stage	Observational (NACC-UDS, cohort); 1 study in similar population	24	1	fair	low
Risk of AEs due to treatment (MCI &AD)	Observational (systematic review); 3 studies in similar population	38	1	poor	low
Probability of withdrawal due to AE	Observational (systematic review); 13 studies in similar population	37	1	good	low
Relative risk					
ChEIs efficacy on MCI patients	Observational (systematic review); 4 studies in similar population	20	1	good	low
Donepezil efficacy on AD patients	RCT (2 years); 1 study in similar population	35	1	low	low
AEs associated with ChEIs (MCI)	Observational (systematic review); 5studies in similar population	20	1	good	low
AEs associated with ChEIs (AD)	Observational (systematic review); 13 studies in similar population	37	1	good	low
Cost (annual)					
CSF biomarker testing	Observational; Centers for Medicare & Medicaid Services	67	1	good	low
Donepezil	Observational		1	good	low
Other costs related to the treatment	Observational; 1 study in dissimilar population	31	1	fair	low
AD costs (formal and informal; community and nursing home)	Observational; 1 study in similar population	55	1	fair	low
MCI direct costs	Observational; 1 study in similar population but conducted in Germany	65	1	poor	low

Appendix 3.A Continued.

Parameter	Data Source	Reference	Strength of evidence		
			Study design ^a	internal validity ^b	external validity ^c
Utility					
MCI	Observational; 1 study in similar population	41	1	fair	low
AD (mild, moderate, and severe) by residential setting (community or nursing home)	Observational; 1 study in similar population	41	1	fair	low
AE	Observational; 1 study in dissimilar population	43	1	poor	low
Donepezil effect duration	Observational (systematic review); 3 studies in similar population	20	1	good	low

^aObservational studies qualify as level 1 if they are used to estimate a parameter that cannot be determined experimentally (for example, mortality rate due to age-, sex-, and race-related causes).

^bInternal validity is the degree to which the study provides valid evidence for the population and setting in which it was conducted.⁸¹

^cExternal validity is the extent to which the evidence is relevant and generalizable to the population and conditions of typical primary care practice.

Abbreviation: AD, Alzheimer's disease; MCI, mild cognitive impairment; CSF, cerebrospinal fluid; AEs, adverse events; ChEIs, cholinesterase inhibitors; ADNI, Alzheimer's disease neuroimaging initiative; NACC-UDS, uniform data set of the national Alzheimer coordinating center; CERAD, Consortium to Establish a Registry for Alzheimer's disease; RCT, randomized clinical trial.

Appendix 3.B Annual transition probabilities (combined stage and nursing home transitions) between disease severity and residential settings, adapted from Spackman et al.'s study.^{*,24}

Time (t)	Time (t+1)						Institutionalization
	Mild/Com	Mild/NH	Mod/Com	Mod/NH	Sev/Com	Sev/NH	
Mild/Com	0.809	0.010	0.165	0.002	0.014	0.0002	0.012
Mild/NH		0.819		0.167		0.014	
Mod/Com			0.677	0.024	0.289	0.010	0.034
Mod/NH				0.701		0.299	
Sev/Com					0.934	0.066	0.066
Sev/NH						1	

*The table presents the combined stage and nursing home transition matrix, obtained by multiplying stage-to-stage and stage-to-nursing home transitions for each possible combination of disease severity and residential settings. For example, patients who begin in the mild/community state have a 80.9% chance ($0.819 \times [1-0.012]$) of remaining in that state in the following year. These combined transition probabilities were computed conditional on being alive in the beginning of the following year.

Abbreviation: Com, community; NH: nursing home; Mod, moderate; Sev, severe.

Appendix 3.C Summary of previous meta-analyses on treatment efficacy of the use of cholinesterase inhibitors in patients with mild cognitive impairment.

Author, Year	Interventions	Included Studies, N	Total Subjects	Measurement	Treatment efficacy*	Conclusion
Sobow, ^{21†} 2007	ChEIs	4	3,429	CDR = 0.5	GAL-INT-11 (2001): OR= 0.7 (0.5-1) [galantamine] GAL-INT-18 (2001): OR= 0.8 (0.6-1.1) [galantamine] InDDEX (1999): OR= 0.8 (0.6-1.1) [rivastigmine] Petersen (2005): OR= 0.8 (0.5-1.2) [donepezil] Overall: OR= 0.8 (0.6-0.9)	The use of ChEIs resulted in approximately 24% reduction of risk of conversion from MCI to dementia.
Raschetti, ¹⁹ 2007	ChEIs	8 (3 primary publications, 5 RCT registers)		CDR=0.5 MMSE >26	InDDEX (1999): OR= 0.85 (0.64-1.12) Petersen (2005): OR= 0.84 (0.57-1.25)	The use of ChEIs in MCI was not associated with any delay in the onset of AD.
Diniz, ^{17†} 2009	ChEIs	4	3,574	CDR = 0.5 or MMSE = 24-30	Winblad 1 (2008): RR= 0.60 (0.43 – 0.83) [galantamine] Winblad 2 (2008):RR=0.72 (0.55 – 0.95) [galantamine] Feldman (2007): RR=0.81 (0.63 – 1.04) [rivastigmine] Petersen (2005): RR= 0.88 (0.66 - 1.18) [donepezil] Overall: RR= 0.75 (0.66-0.8)	The long-term use of ChEIs in subjects with MCI may attenuate the risk of progression to AD/dementia.
Birk (CR), ¹⁸ 2010	Donepezil	3	782	MMSE > 23	1st study: MD (ADAD-Cog)= 1.9 (0.51-3.29) at week 24 Thal (1999): OR= 0.39 (0.21-0.72) at yr1; OR=0.84 (0.57-1.25) at yr3	There is no evidence to support the use of donepezil for patients with MCI.
Russ (CR), ²⁰ 2012	ChEIs	9	5,149	CDR = 0.5 or MMSE = 24-30	Year 1: RR=0.69 (0.47-1) [Petersen 2005; Winblad study 1 & 2 (2008)] Year 2: RR=0.67 (0.55-0.83) [Winblad study 1 & 2 (2008)] Year 3: RR=0.84 (0.7-1.02) [Petersen 2005; Fieldman 2007]	There is very little evidence that ChEIs affect progression to dementia or cognitive test scores in MCI.

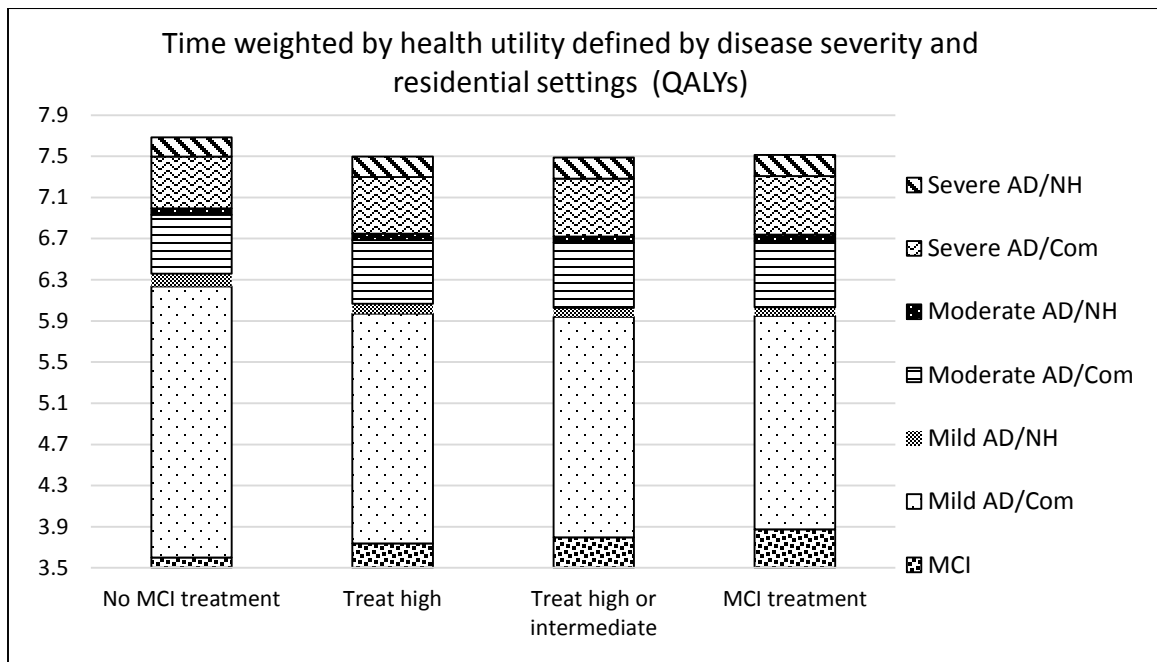
*95 % confidence interval was included in parenthesis.

†included same RCTs.

Abbreviation: CR, Cochrane reviews; ChEIs, cholinesterase inhibitors; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination; OR, odd ratio; RR, relative ratio; MD, mean difference.

Appendix 3.D Discounted quality-adjusted life years (QALYs) (weighted time) by disease severity (MCI, mild, moderate and severe AD) and residential settings (community and nursing home).

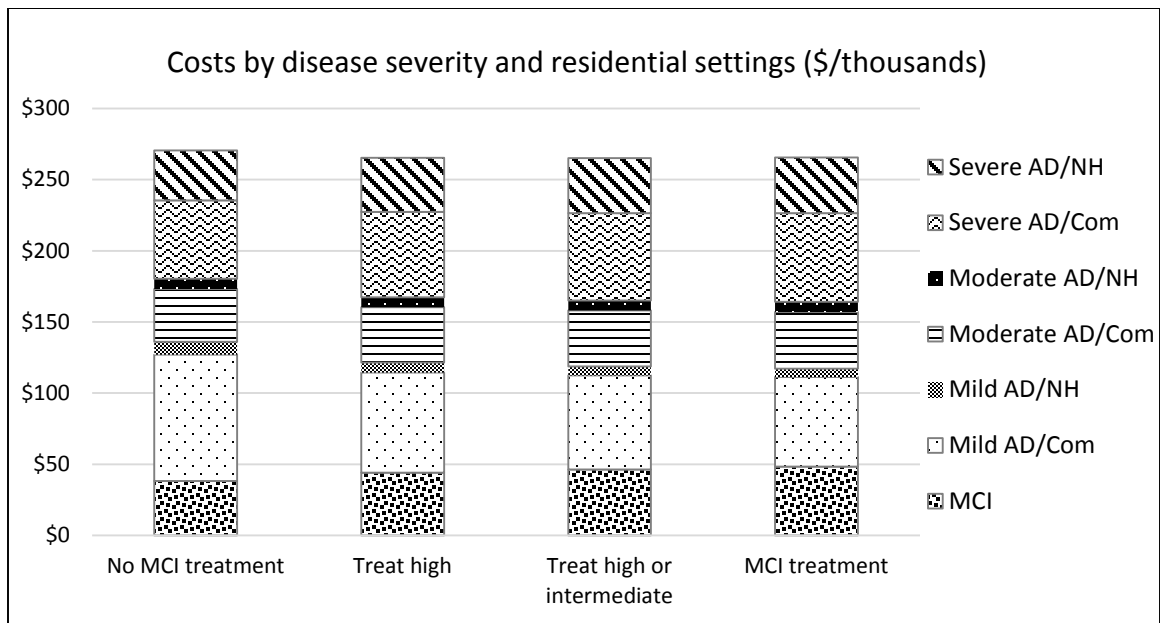
We decomposed the total QALYs (with a discount rate of 3% per year) generated by each strategy by different disease severity and residential settings. Treating all MCI patients but treatment stops when they convert to AD (MCI treatment) demonstrated the greatest gain of AD-free life years but a relatively shorter quality-adjusted time spent in the mild AD/community state, whereas treating only when MCI patients convert to AD (MCI treatment) exhibited the longest time in the mild AD/community state. The difference of QALYs among each treatment strategy seemingly represented the trade-off of weighted time (by health utility and discount rate) spent between the MCI state and mild AD/community state. Admittedly, the amount of time spent in terms of the disease severity regardless of residential settings (assumed that care components were not varied by where patients dwelled) appears to drive the difference of costs incurred by each health state (Markov state) between treatment strategies because it is believed that healthcare costs are positively associated with disease severity.



AD, Alzheimer's disease; QALYs, quality-adjusted life years; MCI, mild cognitive impairment; Com, community; NH, nursing home.

Appendix 3.E Discounted lifetime costs accumulated of strategies by disease severity (MCI, mild, moderate and severe AD) and residential settings (community and nursing home).

As expected, the cost acquired in each health state (Markov state) defined by disease severity and residential setting of each strategy was associated with QALYs accumulated in that state. The cost incurred for patients with mild AD living in the community was inversely related to the cost for patients with severe AD living in the community conditional on the proportion of MCI patients received treatment before they convert to AD. Specifically, with more MCI patients received treatment, the less cost accrued in the mild AD/community state but more in the MCI and severe AD/community states. Across all health states, costs of medication for MCI or AD patients constituted a very small proportion of the total amount of costs; the costs of pharmaceuticals accounted for 3-4% of total costs across different treatment strategies.



AD, Alzheimer’s disease; MCI, mild cognitive impairment; Com, community; NH, nursing home. Discount rate was 3% per year.

Appendix 3.F One-way deterministic sensitivity analysis of no MCI treatment versus MCI treatment on the treatment effectiveness for MCI patients.*

Treatment effectiveness for MCI patients (RR)	ΔCost(\$)	ΔQALY	ICER (\$/QALY) [†]	Optimal strategy
0.76	7,334	0.126	58,100	MCI treatment
0.77 [§]	7,102	0.134	53,000	MCI treatment
0.78	6,872	0.142	48,500	No MCI treatment
0.79	6,642	0.149	44,500	No MCI treatment
0.80	6,413	0.157	40,900	No MCI treatment
0.81	6,185	0.165	37,600	No MCI treatment
0.82	5,958	0.172	34,600	No MCI treatment
0.83	5,732	0.180	31,900	No MCI treatment
0.84 [¶]	5,506	0.187	29,400	No MCI treatment

*No MCI treatment strategy is cost-effective if an ICER is less than \$50,000/QALY.

[§]The threshold that the optimal strategy changed.

[¶]The value used in the base-case analysis.

[†]The value was rounded to the nearest \$100.

Abbreviation: MCI, mild cognitive impairment; QALY, quality-adjusted life year; RR, relative risk; ICER, incremental cost-effectiveness ratio.

Appendix 3.G One-way deterministic sensitivity analysis of no MCI treatment versus MCI treatment on the treatment effectiveness for patients with mild AD.*

Treatment effectiveness for patients with mild AD (RR)	ΔCost(\$)	ΔQALY	ICER (\$/QALY) [†]	Optimal strategy
0.58 [¶]	5,506	0.187	29,400	No MCI treatment
0.59	5,466	0.176	31,100	No MCI treatment
0.60	5,425	0.165	33,000	No MCI treatment
0.61	5,384	0.153	35,100	No MCI treatment
0.62	5,343	0.142	37,500	No MCI treatment
0.63	5,303	0.132	40,300	No MCI treatment
0.64	5,262	0.121	43,600	No MCI treatment
0.65	5,222	0.110	47,400	No MCI treatment
0.66 [§]	5,181	0.099	52,100	MCI treatment
0.67	5,141	0.089	57,800	MCI treatment
0.68	5,101	0.079	64,900	MCI treatment

*No MCI treatment strategy is cost-effective if an ICER is less than \$50,000/QALY.

[§]The threshold that the optimal strategy changed.

[¶]The value used in the base-case analysis.

[†]The value was rounded to the nearest \$100.

Abbreviation: AD, Alzheimer's disease; MCI, mild cognitive impairment; QALY, quality-adjusted life year; RR, relative risk; ICER, incremental cost-effectiveness ratio.

Appendix 3.H One-way deterministic sensitivity analysis of no MCI treatment versus MCI treatment on the excess mortality rate due to AD.*

Excess mortality due to AD	Δ Cost(\$)	Δ QALY	ICER(\$/QALY) [†]	Optimal strategy
0.11 [¶]	5,506	0.187	29,400	No MCI treatment
0.13	6,875	0.198	34,800	No MCI treatment
0.15	8,016	0.207	38,800	No MCI treatment
0.17	8,979	0.214	41,900	No MCI treatment
0.19	9,799	0.221	44,300	No MCI treatment
0.21	10,504	0.227	46,300	No MCI treatment
0.23	11,115	0.232	47,900	No MCI treatment
0.25	11,650	0.237	49,200	No MCI treatment
0.27 [§]	12,121	0.241	50,300	MCI treatment

*No MCI treatment strategy is cost-effective if an ICER ratio is less than \$50,000/QALY.

[§]The threshold that the optimal strategy changed.

[¶]The value used in the base-case analysis.

[†]The value was rounded to the nearest \$100.

Abbreviation: AD, Alzheimer's disease; MCI, mild cognitive impairment; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

Appendix 3.I One-way deterministic sensitivity analysis of cost-effectiveness results on the risk of progression from MCI to AD.*

Multiplier of risk on the progression to AD [‡]	ΔCost(\$)	ΔQALY	ICER(\$/QALY) [†]	Optimal strategy
0.1	11,395	0.484	23,500	MCI treatment
0.2	7,642	0.302	25,300	MCI treatment
0.3	4,688	0.174	27,000	MCI treatment
0.4	2,326	0.080	29,100	MCI treatment
0.5 [§]	404	0.009	46,700	MCI treatment
0.6	1,186	0.047	25,100	No MCI treatment
0.7	2,523	0.092	27,400	No MCI treatment
0.8	3,663	0.129	28,300	No MCI treatment
0.9	4,647	0.161	29,000	No MCI treatment
1.0 [¶]	5,506	0.187	29,400	No MCI treatment
1.1	6,264	0.210	29,800	No MCI treatment

*The ICER was calculated of MCI treatment versus no MCI treatment when the multiplier was < 0.6 (MCI treatment is cost-effective if an ICER is less than \$50,000/QALY), whereas it was calculated of no MCI treatment versus MCI treatment when the multiplier was ≥ 0.6 (no MCI treatment strategy is cost-effective if an ICER is less than \$50,000/QALY).

§The threshold that the optimal strategy changed.

¶The value used in the base-case analysis.

†The value was rounded to the nearest \$100.

‡We used the multiplier to conduct the sensitivity analysis on the risk of progression from MCI to AD. For example, the risk of MCI patients with high-risk was $0.244 \times 0.6 = 0.146$ when the multiplier is 0.6.

Abbreviation: AD, Alzheimer's disease; MCI, mild cognitive impairment; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

Appendix 3.J One-way deterministic sensitivity analysis of no MCI treatment versus MCI treatment on the treatment effect duration on MCI patients.*

Treatment effect duration	ΔCost(\$)	ΔQALY	ICER (\$/QALY) [†]	Optimal strategy
3 [¶]	5,506	0.187	29,400	No MCI treatment
4	4,258	0.143	29,700	No MCI treatment
5	3,249	0.108	30,100	No MCI treatment
6	2,430	0.079	30,600	No MCI treatment
7	1,760	0.056	31,400	No MCI treatment
8	1,211	0.037	32,700	No MCI treatment
9	759	0.021	35,700	No MCI treatment
10	386	0.008	46,300	No MCI treatment

*No MCI treatment strategy is cost-effective if an ICER is less than \$50,000/QALY.

[¶]The value used in the base-case analysis.

[†]The value was rounded to the nearest \$100.

Abbreviation: MCI, mild cognitive impairment; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

Appendix 3.K One-way deterministic sensitivity analysis of no MCI treatment versus MCI treatment on the annual cost of medication.*

Annual costs of medication (\$)	Δ Cost(\$)	Δ QALY	ICER(\$/QALY) [†]	Optimal strategy
100	1,867	0.187	10,000	No MCI treatment
1,000	3,061	0.187	16,400	No MCI treatment
1,500	3,724	0.187	19,900	No MCI treatment
2,000	4,387	0.187	23,400	No MCI treatment
2,500	5,050	0.187	27,000	No MCI treatment
2,844 [¶]	5,506	0.187	29,400	No MCI treatment

*No MCI treatment strategy is cost-effective if an ICER is less than \$50,000/QALY.

[¶]The value used in the base-case analysis.

[†]The value was rounded to the nearest \$100.

Abbreviation: MCI, mild cognitive impairment; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

Appendix 3.L One-way deterministic sensitivity analysis of no MCI treatment versus MCI treatment on the time horizon of the analysis.*

Time horizon (year)	ΔCost(\$)	ΔQALY	ICER(\$/QALY [†])	Optimal strategy
10	416	0.045	9,300	No MCI treatment
15	1,779	0.118	15,100	No MCI treatment
20	3,564	0.170	21,000	No MCI treatment
25	4,919	0.190	25,800	No MCI treatment
30	5,451	0.192	28,400	No MCI treatment
35 [‡]	5,506	0.187	29,400	No MCI treatment

*No MCI treatment strategy is cost-effective if an ICER is less than \$50,000/QALY.

[†]The value used in the base-case analysis.

[‡]The value was rounded to the nearest \$100.

Abbreviation: MCI, mild cognitive impairment; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

Appendix 3.M Optimal strategy based on the two-way deterministic sensitivity analysis of treatment effectiveness for MCI patients versus treatment effectiveness for patients mild AD.*

Treatment effectiveness for MCI patients (RR)	Treatment effectiveness for patients with mild AD (RR)							
	0.59	0.6	0.61	0.62	0.63	0.64	0.65	0.66
0.75	Treat	Treat	Treat	Treat	Treat	Treat	Treat	Treat
0.76	Treat	Treat	Treat	Treat	Treat	Treat	Treat	Treat
0.77	Treat	Treat	Treat	Treat	Treat	Treat	Treat	Treat
0.78	Treat	Treat	Treat	Treat	Treat	Treat	Treat	Treat
0.79	No treat	Treat	Treat	Treat	Treat	Treat	Treat	Treat
0.80	No treat	No treat	Treat	Treat	Treat	Treat	Treat	Treat
0.81	No treat	No treat	No treat	Treat	Treat	Treat	Treat	Treat
0.82	No treat	No treat	No treat	No treat	No treat	Treat	Treat	Treat
0.83	No treat	No treat	No treat	No treat	No treat	No treat	Treat	Treat
0.84 [†]	No treat	No treat	No treat	No treat	No treat	No treat	No treat	Treat

*No MCI treatment strategy is cost-effective if an incremental cost effectiveness ratio is less than \$50,000/QALY.

[†]The value used in the base-case analysis.

Abbreviation: AD, Alzheimer’s disease; MCI, mild cognitive impairment; QALY, quality-adjusted life year; RR, relative risk; No treat, the no MCI treatment strategy; treat, the MCI treatment strategy.

Appendix 3.N Optimal strategy based on the two-way deterministic sensitivity analysis of the treatment effect duration vs. treatment effectiveness for patients with mild AD.*

Treatment effect duration on MCI patients	Treatment effectiveness for patients with mild AD (RR)					
	0.58 [†]	0.59	0.6	0.61	0.62	0.63
3 [†]	No treat	No treat	No treat	No treat	No treat	No treat
4	No treat	No treat	No treat	No treat	No treat	No treat
5	No treat	No treat	No treat	No treat	No treat	Treat
6	No treat	No treat	No treat	Treat	Treat	Treat
7	No treat	No treat	Treat	Treat	Treat	Treat
8	No treat	No treat	Treat	Treat	Treat	Treat
9	No treat	Treat	Treat	Treat	Treat	Treat
10	No treat	Treat	Treat	Treat	Treat	Treat

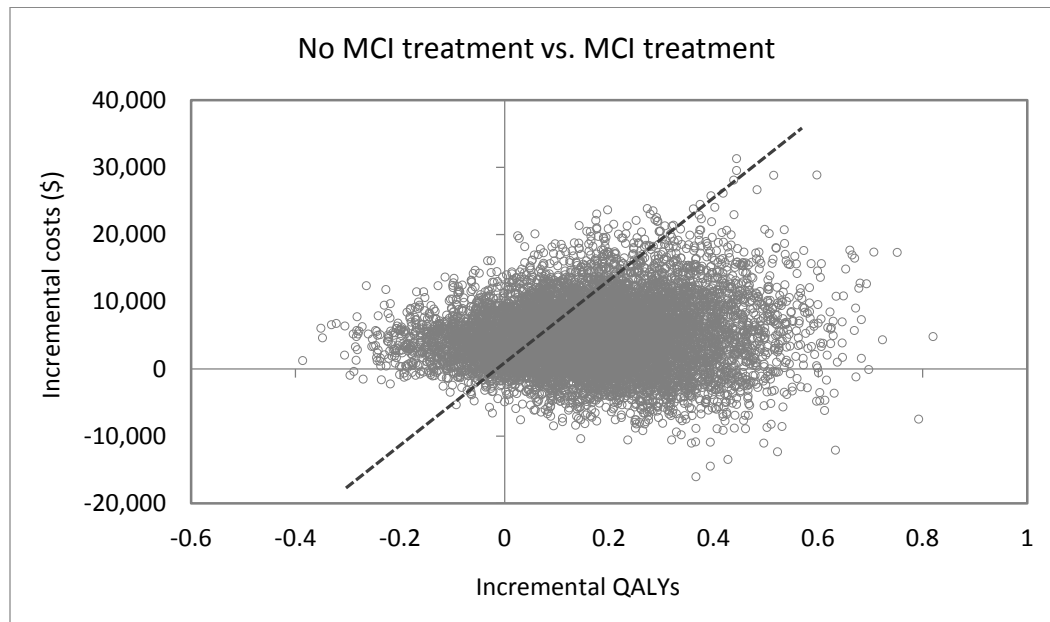
*No MCI treatment strategy is cost-effective if an incremental cost effectiveness ratio is less than \$50,000/QALY.

[†]The value used in the base-case analysis.

Abbreviation: AD, Alzheimer’s disease; MCI, mild cognitive impairment; QALY, quality-adjusted life year; RR, relative risk; ICER, incremental cost-effectiveness ratio; No treat, the no MCI treatment strategy; treat, the MCI treatment strategy.

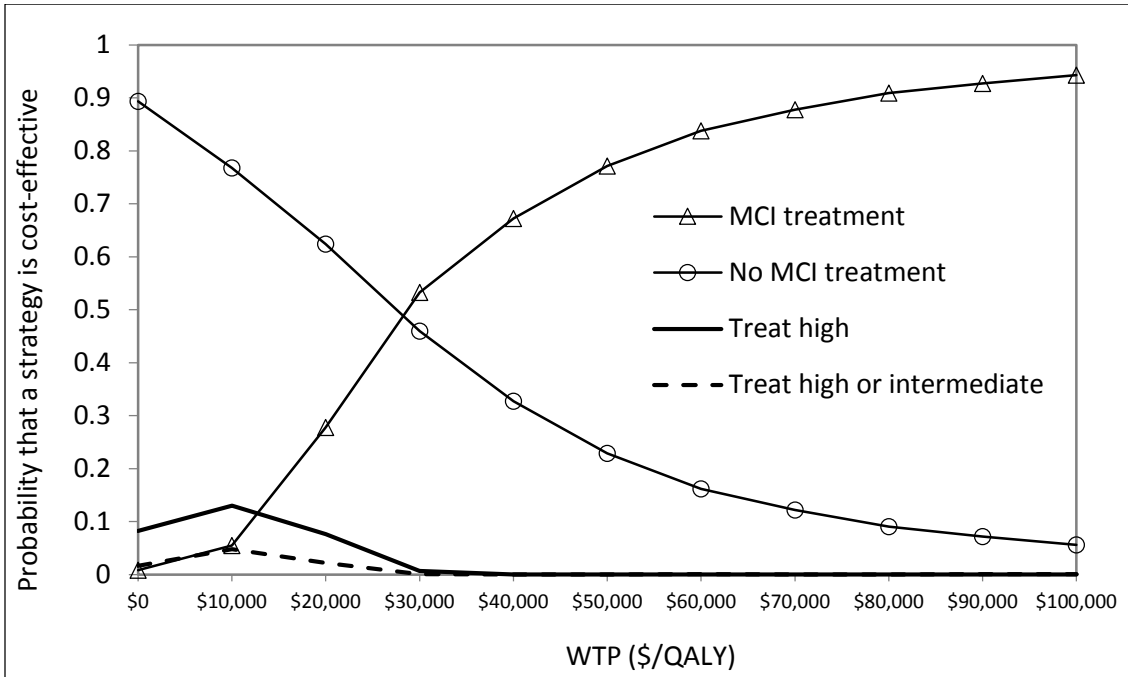
Appendix 3.O Monte Carlo simulation (n=10,000) results on the incremental cost-effectiveness plane. The diagonal dashed-line represents a cost per QALY gained of \$50,000.

According to the theory of cost-effective resource allocation,⁸² the strategy of no MCI treatments is preferred for all points below the dashed line in the northeast quadrant or all points above the dashed line in the southwest quadrant. The No MCI treatment strategy is also preferred for all points in the southeast quadrant, while treating all MCI patients (MCI treatment) is preferred for all points in the northwest quadrant, all points below the dashed line in the southwest quadrant or all points above the dashed line in the northeast quadrant.



MCI, mild cognitive impairment; QALYs, quality-adjusted life years.

Appendix 3.P Cost-effectiveness acceptability curve of the best-case scenario that treat AD patients regardless if they received the treatment in the MCI stage or not.



AD, Alzheimer's disease; MCI, mild cognitive impairment; QALYs: quality-adjusted life years; WTP: willingness to pay.

Appendix 3.Q One-way deterministic sensitivity analysis of MCI treatment versus no MCI treatment on the treatment effectiveness for MCI patients in the best-case scenario.*

Treatment effectiveness for MCI patients (RR)	ΔCost(\$)	ΔQALY	ICER(\$/QALY) [†]	Optimal strategy
0.84 [¶]	4,566	0.163	28,100	MCI treatment
0.85	4,820	0.156	30,900	MCI treatment
0.86	5,072	0.150	33,900	MCI treatment
0.87	5,324	0.143	37,200	MCI treatment
0.88	5,575	0.136	40,900	MCI treatment
0.89	5,825	0.130	44,800	MCI treatment
0.90	6,074	0.123	49,200	MCI treatment
0.91 [§]	6,322	0.117	54,000	No MCI treatment
0.92	6,569	0.111	59,400	No MCI treatment
0.93	6,815	0.104	65,400	No MCI treatment
0.94	7,060	0.098	72,200	No MCI treatment

*The best-case scenario means treating patients both in the MCI and AD stages. MCI treatment is cost-effective if an ICER is less than \$50,000/QALY.

[§]The threshold that the optimal strategy changed.

[¶]The value used in the base-case analysis.

[†]The value was rounded to the nearest \$100.

Abbreviation: AD, Alzheimer's disease; MCI, mild cognitive impairment; QALY, quality-adjusted life year; RR, relative risk; ICER, incremental cost-effectiveness ratio.

Appendix 3.R One-way deterministic sensitivity analysis of varying the parameter of the treatment effectiveness for patients with mild AD in the MCI treatment strategy compared to the fixed effectiveness for the strategy of no MCI treatment in the best-case scenario.*

Treatment effectiveness for patients with mild AD (RR)	ΔCost(\$)	ΔQALY	ICER(\$/QALY) [†]	Optimal strategy
0.58 [¶]	4,566	0.163	28,100	MCI treatment
0.59	4,532	0.153	29,700	MCI treatment
0.60	4,497	0.143	31,500	MCI treatment
0.61	4,463	0.133	33,500	MCI treatment
0.62	4,429	0.123	35,900	MCI treatment
0.63	4,395	0.114	38,600	MCI treatment
0.64	4,360	0.104	41,800	MCI treatment
0.65	4,326	0.095	45,600	MCI treatment
0.66 [§]	4,292	0.085	50,200	No MCI treatment
0.67	4,258	0.076	55,800	No MCI treatment
0.68	4,225	0.067	62,900	No MCI treatment

*The best-case scenario means treating patients when they convert to AD regardless if they have received treatment in the MCI stage or not. MCI treatment with varying treatment effectiveness for patients with mild AD is cost-effective if an ICER is less than \$50,000/QALY.

§The threshold that the optimal strategy changed.

¶The value used in the base-case analysis.

†The value was rounded to the nearest \$100.

Abbreviation: AD, Alzheimer's disease; MCI, mild cognitive impairment; QALY, quality-adjusted life year; RR, relative risk; ICER, incremental cost-effectiveness ratio.

Appendix 3.S Cost-effectiveness results of including strategies of treating MCI patients at low risk and treating MCI patients at low or intermediate risk.*

Strategy [§]	Cost (\$)	QALYs	ICER (\$/QALY) [¶]
Treat high or intermediate	265,211	7.487	
Treat high	265,445	7.499	Weakly dominated
MCI treatment	265,665	7.515	16,500
No MCI treatment	270,609	7.683	29,400
Treat low or intermediate	271,460	7.699	Weakly dominated
Treat low	271,694	7.710	39,500

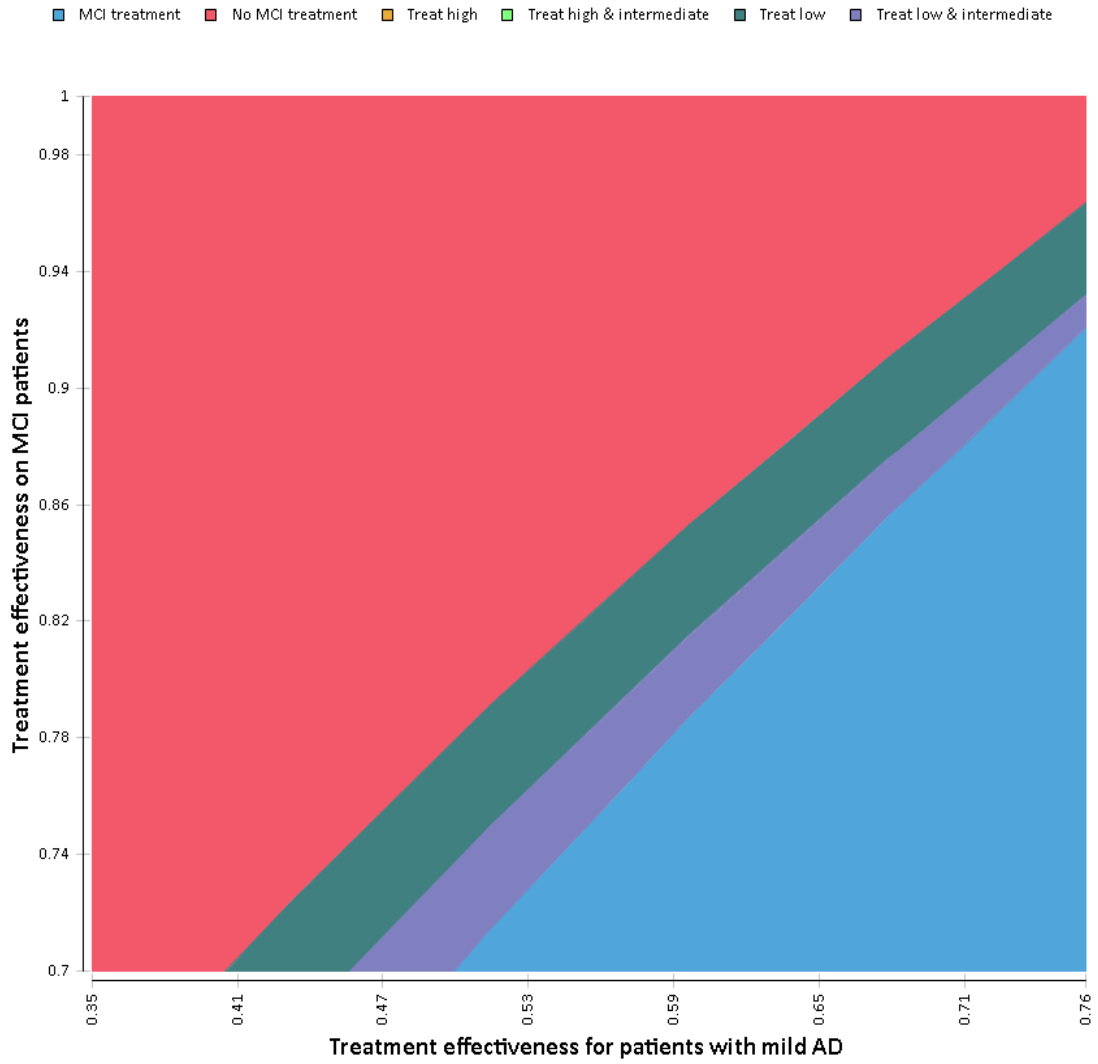
*If MCI patients received treatment, no treatment was provided when they convert to AD.

[§]MCI treatment stands for treating all MCI patients, treat high was treating MCI patients at high risk, treat high or intermediate was treating MCI patients at high or intermediate risk, treat low was treating MCI patients at low risk, treat low or intermediate was treating MCI patients at low or intermediate risk, and no MCI treatment was no treatment on all MCI patients until they convert to AD (based on clinical expert opinion).

[¶]The value was rounded to the nearest \$100.

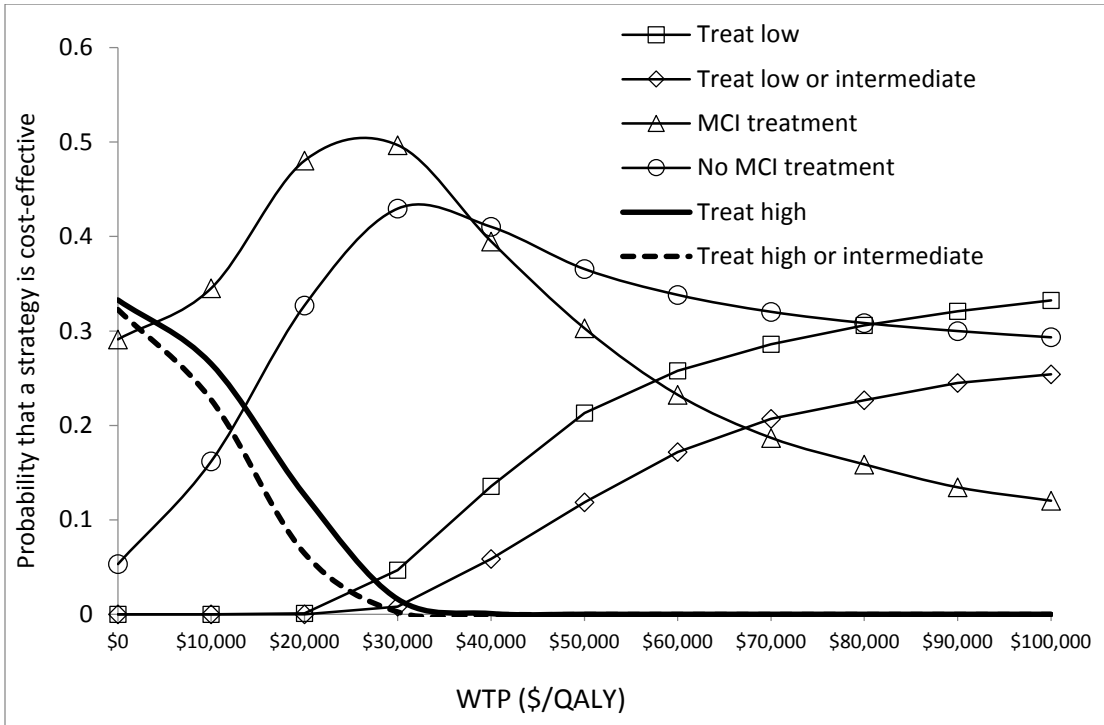
Abbreviation: CSF, cerebrospinal fluid; MCI, mild cognitive impairment; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

Appendix 3.T Two-way sensitivity analysis of treatment effectiveness for mild AD patients vs. treatment effectiveness on MCI patients.



AD, Alzheimer's disease; MCI, mild cognitive impairment.

Appendix 3.U Cost-effectiveness acceptability curve of including strategies of treating MCI patients at low risk and treating MCI patients at low or intermediate risk.



MCI, mild cognitive impairment; QALYs, quality-adjusted life years; WTP, willingness to pay.

Appendix 3.V Cost-effectiveness results of allowing treatments in both MCI and AD stages (best-case scenario).*

Strategy [§]	Cost (\$)	QALYs	ICER (\$/QALY) [¶]
No MCI treatment	270,609	7.683	
Treat high	272,662	7.748	Weakly dominated
Treat low	272,806	7.750	Weakly dominated
Treat high or intermediate	274,012	7.793	Weakly dominated
Treat low or intermediate	274,156	7.794	Weakly dominated
MCI treatment	275,579	7.860	28,100

[§]MCI treatment stands for treating all MCI patients, treat high was treating MCI patients at high risk, treat high or intermediate was treating MCI patients at high risk or intermediate risk, and no MCI treatment was no treatment on all MCI patients until they convert to AD (based on clinical expert opinion).

[¶]The value was rounded to the nearest \$100.

Abbreviation: MCI, mild cognitive impairment; AD, Alzheimer's disease; ICER, incremental cost-effectiveness ratio.

**Chapter 4. Value of Information Analysis to Explore the
Uncertainty of an Early Identification Model of Alzheimer's
Disease**

Brief overview

Objective: To estimate the societal value of reducing uncertainty in a decision whether or not to use cerebrospinal fluid biomarker (CSF) testing to target early treatments for patients with mild cognitive impairment (MCI) who are at risk of developing Alzheimer's disease (AD).

Methods: We used a previously developed model that evaluated the cost-effectiveness of different test-and-treat strategies for MCI patients. CSF biomarker testing categorized patients into risk groups to target treated with cholinesterase inhibitors (ChEIs) for a subset of patients. We used value of information analysis (VOI) to quantify the expected gain from reducing parameter uncertainty associated with these test-and-treat strategies. We derived the expected value of perfect information (EVPI) for all input parameters or a single parameter (partial EVPI), as well as the corresponding expected value of sampling information (EVS), and computed the optimal sample sizes for additional research through the expected net benefit of sampling (ENBS) for those parameters. To demonstrate the use of the EVS and the ENBS to determine the optimal sample size of a new study, we assumed that a fixed cost of \$10 million and a variable cost of \$2,000 per patient for a study collecting data on all parameters. If data on only one parameter was to be collected, we assumed a fixed cost of \$5 million and a variable cost of \$1,000 per patient.

Results: The total EVPI was \$2,122 per patient. The parameters of treatment effectiveness for patients with mild AD and treatment effectiveness for MCI patients were most responsible for uncertainty in the decision model (partial EVPI = \$1,300 and \$820, respectively). A maximum ENBS of \$29 million was reached with an optimal sample size of 1,700 patients for a new study to inform the parameter of treatment effectiveness on patients with mild AD. A study collecting data on the treatment effectiveness for MCI

patients would have an optimal sample size of 3,000 patients and a maximized ENBS of \$ 7 million.

Conclusions: Given our estimates of study costs, the efficient study design for the use of CSF biomarker testing on MCI patients for targeted early treatment involves a trial of 1,700 patients on treatment effectiveness for patients with mild AD and a trial of 3,000 patients on treatment effectiveness for MCI patients, both using ChEIs. VOI analysis provides value-based information in addition to the typical sensitivity analysis (deterministic or probabilistic) to examine the importance of input parameters.

4.1 Introduction

Decision analysis provides a method to systematically incorporate current evidence in order to inform healthcare decisions such that patients' expected outcomes are maximized. The results of a decision analysis can inform the best course of action if the decision were to be made today. However, we know that even the best available evidence is associated with various degrees of uncertainty, which in turn can have implications on the degree of certainty one has with respect to healthcare decisions.¹ While all decisions are associated with various levels of uncertainty, it is important to keep in mind that decisions still have to be made (i.e., "not making a decision" is a decision).

The evaluation of uncertainty in the field of medical decision making is receiving increasing attention.²⁻⁴ In general, decision makers should prefer the alternative that maximizes the expected value of outcome of interests in a decision problem. The outcome of interest could be life expectancy, avoidable hospital admission averted, net health benefits and so on, depending on the perspective of the decision maker. Increased uncertainty surrounding a particular problem increases the concern that the decision maker is making the right decision and also influences their perception of the necessity for further research.⁵ Decisions based on existing information are associated with uncertainty and thus there is always a chance that a wrong decision will be made. This, in turn, may have health- and cost-related consequences (opportunity loss from making a wrong decision). In order to gain more confidence in making the decision, conduction additional research to obtain more information⁶ about the key components that are influential to the decision-making process is considered. The necessity to conduct further research is usually greater when the chosen decision is sensitive to those key components. Consequently, the question is whether or not the decision should be made based on current information or whether or not it is worth investing in additional

data collecting exercise to reduce uncertainty before revisiting the decision.⁷ An approach to ascertain this question is to quantify the expected value gained from reducing uncertainty in a decision problem through additional research⁸ and then evaluate whether it is justified by means of value of information (VOI) analysis.

VOI analysis is a quantitative method which can be used to estimate the cost-effectiveness of a new proposed research project.⁷ The expected value gained from additional research is equal to the expected loss (i.e., poorer patient outcomes) from making a wrong decision due to uncertainty of input parameters in a decision model.⁶ This expected value is compared with the expected cost of a proposed research project to decide the cost-effectiveness of additional research. If the expected value exceeds the (expected) cost the research project should be undertaken.

In the decision analysis whether or not to use cerebrospinal fluid (CSF) biomarker testing on patients with mild cognitive impairment (MCI) for early targeted treatments to delay the progression of Alzheimer's disease (AD), the findings were inconclusive. Using a cost-effectiveness analysis (CEA), in a previous study (Paper 2),⁹ we assessed the six treatment strategies where CSF biomarker information (risk levels of developing AD) was used to decide the treatment threshold for a hypothetical cohort of 65-year-old patients with MCI, which is considered as the prodromal stage of AD. We found CSF biomarker testing seems to add value to the guidance of targeting earlier pharmacological intervention on patients with MCI, especially for those at low risk, but parameter uncertainty on treatment effectiveness for MCI and AD patients is substantial in this case. Before we reach the conclusion for the optimal treatment strategy for MCI patients, VOI analysis provides value-based information for either choosing the strategy based on the current evidence or revisiting the problem after more information is collected. Although previous studies⁶ have conducted VOI analysis on the treatment efficacy of donepezil for AD patients, they did not extend the decision model to

incorporate the prodromal stage of AD and the CSF biomarker information was unavailable to categorize MCI patients into different risk levels of developing AD so that was not accounted for in their study. Thus, the objective of our study was to evaluate the societal value of reducing uncertainty in the early-identification decision model of AD, which was constructed to answer the question whether or not to use CSF biomarker testing to target early treatments for MCI patients in Paper 2. We conducted a VOI analysis to explore uncertainty associated with the input parameters by estimating the value of additional information to better inform the estimates of the existing input parameters used in this decision model. We also extended the scope of this study to include structural uncertainty.

4.2 Methods

A detailed description of the original decision model can be found elsewhere (Paper 2).⁹ Briefly, we developed a state-transition Markov model to project discounted lifetime quality-adjusted life years (QALYs) and costs and then conducted a CEA to evaluate the treatment strategies with and without CSF biomarker testing involved for MCI patients who are at risk of developing AD (**Appendix 4.A**). The treatment strategies (test-treat strategies) including the test results, which was used to stratify MCI patients into risk groups- low, intermediate and high- to decide the treatment strategy, were strategies of: 1) treating MCI patients at low risk (treat low), 2) treating MCI patients at low or intermediate risk (treat low or intermediate), 3) treating MCI patients at high risk (treat high), and 4) treating MCI patients at high or intermediate risk (treat high or intermediate). We also evaluated strategies where no biomarker information was obtained (i.e., no testing strategies); 1) no test and treat only when MCI patients convert to AD (no MCI treatment) and 2) no test and treat all MCI patients (MCI treatment). We assumed that if patients received treatment in the MCI stage, they would not be eligible for treatment when they converted to AD based on clinical expert opinion. In this study, we conducted VOI analysis to estimate the value of reducing uncertainty surrounding input parameters in this decision model to inform additional research decisions, whereas results of CEA from the decision model are used to inform the treatment decision.

4.2.1 Cost-effectiveness analysis

We adopted the net benefit approach to present the results of CEA. Costs and effects (QALYs) were combined into a single outcome:¹⁰ net monetary benefit (NMB) = effect × willingness to pay (WTP) – cost or net health benefit (NHB) = effect – cost/WTP. We used a societal WTP threshold at various levels (up to \$100,000/QALY). The strategy with the maximum net benefit is considered the optimal strategy. In this study, we used

the measure of NMB to present the results of a VOI analysis because it quantifies the expected value of reducing parameter uncertainty in a decision model through additional research. Otherwise, the results were presented as NHB. The principle is similar whether the benefit is cash, utility or some other metric.

We presented the CEA result from a probabilistic analysis to account for the nonlinear feature of Markov model used in the original model, in which the input parameters should ideally be modeled with probability distributions instead of point estimates. Because a model outcome, $f(x)$, when estimated by an approach of a Markov model, is a nonlinear function of uncertain model parameters (x). Accordingly, the expected value of $f(x)$ is not equal to the function of the expected value of x .^{11,12}

4.2.2 Uncertainty analysis

A number of types of uncertainty are relevant to the assessment of the cost-effectiveness of a particular intervention question, including the input parameters, the statistical methods used to estimate the input parameters, the structure of decision-analytical model, and the perspective to a decision question (societal or payer).^{13,14} In this paper, I mainly focused on evaluating uncertainty relevant to input parameters in the decision model, including the chance of making a wrong decision and the consequence associated with it, and the structure of the decision model.

4.2.2.1 Characterization of input parameters information

The characterization of input parameter uncertainty is critical in CEA, particularly when considering the value of conducting additional research.¹³ The result of the base case CEA is affected by the mean of expected outcomes (NMB in our case), which is affected

by the distributions assigned to input parameters, whereas a VOI analysis depends on the distribution of expected outcomes.

The characterization of uncertainty surrounding input parameters in this decision model is summarized in **Table 4.1**. We used data from a longitudinal and observational study- the Alzheimer's Disease Neuroimaging Initiative (<http://adni.loni.usc.edu/>) to estimate the risk of progression from MCI to AD defined by CSF biomarker levels.¹⁵ Treatment efficacy of cholinesterase inhibitors (ChEIs) for MCI patients was obtained from the results of a recent systematic review of 9 clinical control trials¹⁶ with a maximum 3-year study period and the effect was rated as modest, whereas the efficacy for patients with mild or moderate AD was derived from a randomized placebo-controlled double-blind clinical trial (RCT).¹⁷

The annual risk of progression from MCI to AD by CSF biomarker levels was characterized with beta distributions. Beta distributions are commonly used to describe uncertainty of probabilities because they range between 0 and 1. The mean health utility for each health state (Markov state) adopted in the model was characterized with beta distributions with 95% confidence intervals (CIs) based on the lower and upper bound values computed in a similar CEA study.¹⁸ Published data for formal and informal costs for each AD stages, separated by residential settings (community or nursing home), were reported as mean values (μ) only. As a result, we characterized their distribution with a gamma distribution (values are greater than zero and right skewed). We further derived the standard deviation (SD) by assuming the original cost data were normally distributed with 50% less or higher from the same mean as the lower bound (0.5μ) and upper bound (1.5μ) of the 95% CI. Thus, we computed the SD of the assigned gamma distribution for each specified cost parameter associated with AD stages as the mean divided by (2×1.96) . The treatment efficacy for MCI patients was expressed as the relative risk (RR) multiplying with the risk of progression from MCI to AD, so we

characterized the RR with a lognormal distribution based on the reported mean and the CIs from a meta-analysis.¹⁶ On the other hand, the treatment effects for patients with mild or moderate AD were modeled as the RR multiplying with the probabilities of transitions between AD stages, such as from mild to moderate AD and mild to severe AD, or moderate to severe AD. Thus, it was also characterized with a lognormal distribution using information from an RCT.¹⁷ Withdrawal rates due to the treatment associated with adverse events (AEs) either for MCI patients or for AD patients were characterized with beta distributions with the mean and the SD based on the estimates from a meta-analysis.¹⁹

The duration of treatment effect on MCI patients was fixed as constant (3 years) in the base case CEA because the results of a recent meta-analysis of examining ChEI effect on MCI patients only presented 3-year results.¹⁶ In addition, the effect duration on AD patients was assumed to continue until they transition to the severe stage or discontinue due to AEs. The parameter of treatment effect duration on AD patients was found to be the key parameter in a previous CEA²⁰ that this study was adapted to, where the treatment effect duration on AD patients was 24 weeks in the base case analysis and 210 week (about 4 years) in the VOI analysis. In our study, it was calculated as about 5.4 years of treatment for AD patients before they transition to the severe stage based on the parameters applied.

4.2.2.2 Probabilistic sensitivity analysis (parameter uncertainty)

We used the sample (n=10,000), which was generated from a randomly drawn values for each parameter from its assigned probability distribution using a second-order Monte Carlo repeat sampling method, to calculate the base case CEA result, and further performed a probabilistic sensitivity analysis (PSA). We presented PSA results as a cost-effectiveness acceptability curve (CEAC),²¹ which shows the percentage of

iterations that a strategy is optimal (with the highest NHB). Because expected outcomes of costs and QALYs were regenerated for each strategy based on the drawn values of input parameters in each iteration, the output of the PSA provided distributions of costs and QALYS along with distributions of input parameters. We used this output to conduct a VOI analysis in the following section.

4.2.2.3 Value of information analysis (decision uncertainty)

VOI analysis uses Bayesian updating methods to estimate the potential benefits of gathering further information, through more research, to reduce the uncertainty surrounding a decision problem.⁸ The key concept in Bayesian analysis is the updating of a prior belief about plausible values for a input parameter with the support for likely values of that parameter drawn from sampled data (the distribution of which is known as the likelihood function) to form a posterior belief using Bayes theorem.⁷ The results of a data collection exercise (e.g., a clinical trial) are predicted based on current knowledge. These are combined with the current knowledge to predict the state of knowledge (update a degree of belief about an input parameter) after the data are collected.

4.2.2.3.1 Expected value of perfect information - overall uncertainty

In a classic decision analysis, the optimal choice between two or more strategies is the one with the highest expected value of the model outcome.²² The estimates of the expected values are made on the basis of the currently best available data, even though imprecise or incomplete, thus, the outcome result generated with the current evidence is thus referred to as the expected value given current information. The underlying uncertainty in the data introduces the possibility that a decision made based on the current information may not actually be the one with the highest expected value (i.e., it will be the wrong decision). Conversely, it is possible to compute the expected value of

outcomes given perfect information if the optimal decision were known (theoretically) under all possible values for input parameters. The difference between these two expected values (given perfect information vs. given current information) is the expected value of perfect information (EVPI), the upper bound of the expected value from reducing parameter uncertainty in a decision model and the value of collecting data about all input parameters in a hypothetical infinitely large study.²³

Specifically, the EVPI, as shown in Equation 1, is the difference between the expected value of a decision made given perfect information (the first term) about all of the uncertain input parameters θ , which is a vector, and a decision made given current information (the second term).²³ The NMB is the net monetary benefit and the expected outcomes in our decision model and d is the strategy.

$$EVPI = E_{\theta}[\max_d NMB(d, \theta)] - \max_d E_{\theta} NMB(d, \theta) \quad (1)$$

Using a second-order Monte Carlo repeat sampling approach,¹¹ we can rewrite Equation 1 as follows. N stands for the number of model iterations (sampling).

$$\widehat{EVPI} = \frac{1}{N} \sum_{n=1}^N \max_d NMB(d, \theta^{(n)}) - \max_d \frac{1}{N} \sum_{n=1}^N NMB(d, \theta^{(n)})$$

This approach is illustrated in **Appendix 4.B** using a simplified, two alternative strategies, MCI treatment and no MCI treatment, with the expected value of NMB generated for each one. Each iteration consists of drawing a random value for each input parameter from distribution assigned in the PSA.

To determine whether additional data collection might be beneficial, the costs associated with conducting further studies should be compared to the population EVPI.²⁴

Population EVPI places an upper bound on the value of further research for the population that can potential benefit from it. It is calculated by multiplying the EVPI per patient with the number of patients affected by the decision each year (i.e., the annual incidence of new MCI patients in the US) and the projected affected time horizon of the decision.²³ For the US perspective, we estimated the annual population that could potentially benefit from the results of a future study to be 10% of the 162 (range, 122-202) thousand patients with MCI who are 65-year-old using the projection of an incidence rate (60.4, 95%CI: 45.6-75.3 per 1,000 person-years) from the Aging, Demographics, and Memory Study²⁶ along with the 2013 US census data. We assumed that the projected effective lifetime of this decision problem, whether or not to apply CSF biomarker testing on patients with MCI for early targeted treatments, is 2 years and varied it (2-8 years)⁶ in a sensitivity analysis. The computation of the affected population was shown as Equation 2 in which T is the effective lifetime of this decision, I_t is the estimates of incidences over this period, and r is the discount rate which was assumed at a rate of 3% per year.²⁵

$$Population\ EVPI = EVPI \times \sum_{t=1}^T \frac{I_t}{(1+r)^t} \quad (2)$$

4.2.2.3.2 Partial expected value of perfect information

It is often of interest to estimate the EVPI for an individual parameter or sets of parameters (partial EVPI). Partial EVPI is often used to identify the parameters that are most influential (with the highest expected value) to decision uncertainty^{3,23,24} and as such can be used to guide the design and prioritization of future research to better inform the values of these parameters.^{27,28} Again, θ stands for all the uncertain parameters input in our decision model, and can be further divided into θ_i (subsets of

parameters of interest) and θ_{-i} (the complement set of parameters) as shown in Equation 3. Similarly, the NMB stands for the net monetary benefit and is the expected outcomes in our decision model and d is the strategy.

$$Partial\ EVPI = E_{\theta_i}[\max_d E_{\theta_{-i}|\theta_i} NMB(d, \theta_i, \theta_{-i})] - \max_d E_{\theta} NMB(d, \theta) \quad (3)$$

We estimated the partial EVPI for an individual parameter and sets of parameters that were categorized into the cost, QALY, and transition probability groups, to identify either an individual parameter or a set of parameters (θ_i) with the highest expected value regarding decision uncertainty.

Again, with Monte Carlo repeat sampling methods which was used to calculate the EVPI, Equation 2 can be expressed as:

$$partial\ \widehat{EVPI} = \frac{1}{K} \sum_{k=1}^K \max_d \frac{1}{J} \sum_{j=1}^J NMB(d, \theta_i^{(k)}, \theta_{-i}^{(k,j)}) - \max_d \frac{1}{N} \sum_{n=1}^N NMB(d, \theta^{(n)})$$

In the first term, j and k stand for the number of sampling in the inner and outer loops defined in the Monte Carlo repeat sampling method, respectively. In order to calculate the expected value of the NMB based on each parameter set, the outer loop draws the value from the distribution of parameters of interest, whereas the inner loop draws the values from distributions of all the rest parameters. The second term is the same as in Equation 1, but N now is equal to $j \times k$ times model iterations. By sampling the parameter of interest in the outer loop while sampling all the rest parameters in the inner loop simultaneously to control the bias due to the nonlinear feature of Markov model, we computed the partial EVPI as the unbiased expected value of conducting additional

research specifically on the parameters of interest.

Partial EVPI analyses can be computed either using one-level (the outer loop only)⁵ if a decision model come with the linear structure or using two-level (the inner and outer loops together) sampling algorithms.¹² When a model is perfectly linear and no correlation exists between input parameters, the one-level sampling algorithms will provide estimates of the partial EVPI that are equal to the two-level sampling algorithms.²⁷ In our case, nevertheless, this assumption was not fulfilled because of the Markov model feature. An inherent characteristic of a Markov model is the multiplication of matrices with transition probabilities over subsequent cycles, causing the models to be nonlinear.²⁷ The total iterations for a partial EVPI analysis in our case would be j times k when applying two-level methods. This may become the computational burdensome when the number of iteration for inner and outer loops is high.²⁹ To save the computational cost and resolve the possible correlations existing between parameters without using more complicated methods (e.g., Markov chain Monte Carlo [MCMC]), we adopted the nonparametric generalized additive model (GAM) proposed by Strong et al.³⁰ to estimate partial EVPIs.

Specifically, we exported the PSA results (10,000 sets) with sampled input parameters from their assigned distributions and the expected outcomes, expressed as costs and QALYs ,and fitted the model output with the GAM. We particularly focused on the parameters of the treatment efficacy for MCI or AD patients, the risk of progression to AD from MCI, health utilities, and the costs of formal and informal care.

4.2.2.3.3 Expected value of sample information and the optimal sample size

The total EVPI and the partial EVPI are relevant to evaluate the importance of overall uncertainty and identify key parameters responsible for decision uncertainty. However, they are insufficient to justify and guide further research because they are estimated

based on a hypothetical infinitely large sample.³

The expected value of sample information (EVSI) is the expected benefit of reducing uncertainty by obtaining information from a future study, collecting information on all parameters, with a finite sample size.²³ That is, the total EVSI for all input parameters or the partial EVSI for a single parameter or a set of parameters will reach a ceiling: the corresponding EVPI or the partial EVPI of that parameter(s), with the increasing sample size of a new study.³¹ Estimation of the total EVSI or the partial EVSI across a range of sample sizes can allow us to find the optimal sample size in terms of the expected cost of a new study for the key parameters. The key component of computing the EVSI is to use the Bayesian updating procedure and then the existing uncertainty for a single parameter or a set of parameters can be updated from a proposed new study (new evidence) to form a new (updated) distribution for the input parameters.³² The step-by-step algorithm of Bayesian updating procedure to compute the partial EVSI can be found in published studies.^{23,32} However, to use the Bayesian method, we need to specify the distribution not only for the input parameters but also for a new study that will provide the new evidence. It can be challenging if the distribution of new data are not conjugate to the distribution of input parameters, where more complex methods (e.g., MCMC) will be needed.^{23,32} Thus, we used the GAM model³³ mentioned above to estimate the total EVSI and partial EVSI (using the same parameters considered in partial EVPI analyses). We also estimated the partial EVSI for several sets of parameters to assess various study designs aimed at informing a subset of parameters. To compute the EVSI by the GAM model, we still had to assign a distribution for the new data collection based on the type of data collected. We assumed the binomial distribution for studies that update probabilities (e.g. the risk of progression to AD) because the random variable drawn from such distribution is the number of events (patients who have progressed from MCI to AD) in a new study. Analogously, we

assumed the normal, the lognormal, and the binomial distributions for studies on costs, the treatment efficacy, and the health utilities, respectively.

Any effort to improve the quality of available data that costs less than the population EVSI, which is calculated by multiplying the EVSI per patient with the number of patients affected by the decision problem each year (similar to the population EVPI calculation), is worth pursuing.²² That is to say, comparing the population (partial) EVSI with the cost of additional studies that will provide new evidence for an input parameter allows us to determine if the additional research for that parameter is justified. For example, additional research of treatment efficacy either for MCI or AD patients may be justified if the expected value of the population (partial) EVSI exceeds the expected cost of that additional research.

The expected net benefit of sampling (ENBS)^{3,12} as shown in Equation 4, is derived by subtracting the cost of a proposed new study from the population EVSI:

$$ENBS(n) = Population\ EVSI\ (n) - [fixed\ cost + (variable\ cost \times (n))] \quad (4)$$

where n stands for the sample size of a new proposed study and fixed and variable costs are the cost of a proposed new study. If the $ENBS(n) > 0$ for any sample size, then further research is justified.³⁴ The ENBS also provides a framework for the efficient design of a clinical trial. The optimal sample size n^* for a proposed trial is where the ENBS reaches a maximum.³⁵ At this maximum the additional benefit of one more patient in the study equals the additional study costs of one more patient in the study.³¹ To demonstrate the use of the EVSI and the ENBS to determine the optimal sample size for a hypothetical clinical trial collecting data on all parameters (total EVSI), where we assumed a fixed cost of \$10 million and a variable cost of \$2,000 per patient. In practice, this framework could be used to evaluate the sample size of a future study on a specific

input parameter. We assumed a fixed cost of \$5 million and a variable cost of \$1,000 per patient if data on only one parameter (e.g. the treatment efficacy on MCI or AD patients) was to be collected. These assumed cost estimates would need to be updated with further information.

Of note, the ENBS of a proposed new study is not the actual benefit of the study but the expected benefit prior to conducting the study. Unless the result of a new study change the standard of care, the actual benefit to an individual patient is zero. However, a new study will always reduce the uncertainty of the decision.³¹

4.2.2.4 Structural uncertainty

Many of the structural changes made to the decision model can be thought of in terms of missing parameters or parameters assigned a single and often extreme value.^{13,36}

Considering structural uncertainty by parameterizing allows us to more fully characterize the uncertainty in a decision analysis. Accordingly, we presented the CEA result with the assumption that treatment effect duration on MCI patients varied between 3 to 10 years as defined by an uniform distribution comparing with the constant assumption (3 years) in the base case to explore the structural uncertainty.

All analyses were performed in TreeAge (version TreeAge Pro 2013, TreeAge Software, INC, Williamstown, Mass), Microsoft Excel (Microsoft Corp., Redmond, WA), and R software (version 3.0.3; R Foundation for Statistical Computing, Vienna, Austria).

4.3 Results

4.3.1 Cost-effectiveness analysis

Our CEA results were estimated by 10,000 PSA iterations. CEA results indicated the strategies of treat high, and treat high or intermediate were less costly and less effective than two strategies with no testing involved. Treating MCI patients at low risk was cost-effective among all strategies with the highest NHB (2.276 QALYs) (**Table 4.2**).

4.3.2 Probabilistic sensitivity analysis

The chance that a strategy is the optimal strategy is the percentage of PSA simulations where it has the highest NHB. **Figure 4.1** shows that the no MCI treatment strategy was optimal in about 37% of the 10,000 iterations of PSA at WTP of \$50,000/QALY, whereas it was 30% and 21% for treating all MCI patients and treating MCI patients at low risk, respectively. Furthermore, strategies of no MCI treatment and treat low were intersecting at WTP of \$80,000/QALY. Strategies of treat high, and treat high or intermediate showed low chances to be cost-effective compared with strategies of no MCI treatment or MCI treatment. The chance to be cost-effective was even lower when the WTP threshold was higher than \$30,000/QALY.

We further compared MCI treatment and no MCI treatment strategies specifically to explore the structural uncertainty. The incremental net health benefit (INHB) between strategies of MCI treatment and no MCI treatment was 0.07 QALY (95% credible interval, -0.28-0.42) based on the assumption of 3-year treatment effect duration in the MCI stage (**Figure 4.2**). As the treatment effect duration on MCI patients was extended (ranged from 3 to 10 years) in the PSA, the expected INHB was reduced to 0.004 (95% credible interval: -0.41-0.42) and the chance that the no MCI treatment strategy becomes cost-effective also decreased with the treatment effect duration on MCI patients varied from 3 to 10 year while held other parameters constant at their mean

values; however, the uncertainty surrounding the estimates of INHB increased (a flatter distribution, **Figure 4.2**) as the model extrapolated the duration beyond 3 years.

4.3.3 VOI analysis

In the following section, we investigated uncertainty surrounding the input parameters in the decision model constructed in Paper 2, which examined the cost-effectiveness of all six strategies on MCI patients, using a VOI analysis.

4.3.3.1 Total EVPI: overall importance of uncertainty

We found the total EVPI of \$2,122 per patient. This means that after eliminating all the potential parameter uncertainty surrounding the decision model, we can expect an improvement in NMB of \$2,122 per patient. With the annual population that would be affected by this decision was estimated at 16 (95% CI, 12-20) thousand patients with MCI and the assumption that MCI patients would benefit from this decision for 2 years, we found a discounted population to benefit of about 31 (range, 23-39) thousand MCI patients. The resulting population EVPI was about \$658 million, varied by the amount of the affected population (\$496-720 million), or an equivalent benefit of 13,152 QALYs (assuming a WTP of \$50,000 per QALY).

4.3.3.2 Partial EVPI: important parameters

In our study, 11 out of 42 input parameters either derived from the primary data analysis or the published literature had a non-zero partial EVPI. **Figure 4.3** shows that treatment effectiveness for patients with mild AD was the parameter with the highest partial EVPI per patient (\$1,300), second was treatment effectiveness for MCI patients (\$820), and third was the risk of progression to AD for MCI patients at low risk (\$480).

Regardless of the partial EVPI of an individual parameter, we also estimated a

set of parameters by categories, including costs in the AD stage, the treatment effectiveness, and the risk of progression from MCI to AD, respectively. As **Figure 4.4** shown, parameters in the treatment effectiveness category had the highest informational value (\$1,946). The overall risk of progression from MCI to AD had the partial EVPI of \$714, whereas it was \$449 for costs in all AD stages.

4.3.3.3 Total and partial EVSI

We computed the total and partial EVSI for treatment effectiveness for patients with mild AD, treatment effectiveness for MCI patients, the risk of progression from MCI to AD and a set of cost parameters. **Figure 4.5** presents the total EVSI and the partial EVSI of parameters as the function of a sample size (n) if a new study is performed. The total EVSI was about \$2,144 per patient when the sample size was 1,500. Similar to the results of the partial EVPI, the parameter of treatment effectiveness for patients with mild AD had highest partial EVSI along with the increased sample size and reached the plateau approximately when the sample size of a new study was greater than 1,600 (the partial EVSI = \$1,148), whereas treatment effectiveness for MCI patients, the risk of progression from MCI to AD, and the costs in the AD stages reached the maximum expected values while the sample sizes were 1,200, 1,100, and 1,400, respectively. It is evident that the magnitude of uncertainty (the partial EVPI) is positively related to the potential required sample size of a proposed study.

4.3.3.4 ENBS: the optimal sample size

Hypothetically, a clinical trial collecting data on all parameters (total EVSI) provides a framework for calculating the sample size of a new study where the study design and the cost information would be provided by the study investigators. For illustrative purposes we assumed that a fixed cost of \$10 million and a total variable cost of \$2,000 per

patients for a news study of collecting data on all parameters, whereas it was \$5 million of a fixed cost and \$1,000 of a total variable cost for a single parameter. It was estimated about \$97 million from a study³⁷ of estimating the average cost that the firm expects to spend on the drug when it enters Phase I human clinical trials. We used the estimated population, similar to the one in the computation of population EVPI, who would benefit of about 31 (range, 23-39) thousand MCI patients. **Figure 4.6** presents the study costs, the population EVSI, and the ENBS as a function of the sample size (n) of a proposed new study. A maximum ENBS of about \$56 million, varied by the amount of the affected population, was reached for a sample size of about 3,500 MCI patients (the optimal sample size) of a hypothetical new study of all input parameters (not shown). The population EVSI was about 73 million in this case. Moreover, for the parameter of treatment effectiveness for patients with mild AD, the ENBS reached the maximum value (\$ 29 million) at the sample size of 1,700 (**Figure 4.6A**). The optimal sample size for collecting data on treatment effect for MCI patients was \$3,000 patients with ENBS of \$7 million (**Figure 4.6B**).

The sensitivity analyses for the population to benefit of and the study costs on the parameter of treatment effectiveness for patients with mild AD demonstrated that the optimal sample size remained robust of 1,700- 2,000 even if the study costs doubled or was reduced to half (**Table 4.3**).

With the assumption that the duration of the decision problem would affect the population for 8 years, the affected population increased from 31 thousand to about 114 thousand MCI patients but the optimal sample size of a proposed new study of treatment effectiveness for patients with mild AD was still around 1,700 patients (not shown).

4.4 Discussion

In this study, we attempt to estimate the societal value of reducing parameter uncertainty in the decision whether or not to use CSF biomarker testing to target early treatments for patients with MCI given the existing information, and further answer the question whether or not more information is required to inform this decision. According to previous CEA results, treating MCI patients at low risk was cost-effective compared with no MCI treatment, however, there is a possibility that the strategy of no MCI treatment might be cost-effective due to uncertainty of the input parameters in our decision model and when the PSA results indicated that no MCI treatment might have a higher chance to be cost-effective than the treat low strategy. There would be a potential opportunity loss if we did not consider the strategy of no MCI treatment based on the base case result of CEA. It was a 37% chance that no MCI treatment would generate greater net benefits than the 30% of MCI treatment and 21% of the treat low strategy given the existing information at WTP of \$50,000/QALY. The treatment effect duration on MCI patients had little impact here when we modified the model structure by allowing the parameter varied between 3 to 10 years.

Due to the inconsistent results on the base-case CEA and PSA, we applied VOI analysis to determine whether or not the expected value of reducing uncertainty, through more research, of the parameters in our decision model justifies the cost of additional research. We found the population EVPI of \$658 (range by the affected population, \$496-\$820) million. This indicates that if we could eliminate all uncertainty regarding this decision, we would expect a societal financial benefit of about \$658 million, which is equivalent to a societal health benefit of 13,152 QALYs. The population EVPI for this decision measures the maximum possible payoff from a hypothetical research collecting data on all parameters for more precise estimates.⁶ Moreover, it might be feasible to compare the expected societal benefit of \$658 million with the expected societal benefit

of other proposed research projects to set research priorities. The decision uncertainty, measured by the population EVPI, regarding whether or not to use CSF biomarker testing on patients with MCI to decide the optimal treatment strategy turned out to be substantial in contrast to other clinical questions that have been addressed using VOI approach.^{3,6} For example, it was estimated the population EVPI of \$339 million in a study evaluating whether or not to apply donepezil treatment on AD patients⁶ (4-years effect duration) and \$0.5 million of a study to investigate the use magnetic resonance imaging on patients with acute knee trauma in an emergency department setting.³ One of the possible reasons why the substantial difference of the population EVPI between our and their studies may be due to the potential population would be benefit of from the decision question is relatively greater in our study.

Eleven parameters were individually responsible for the decision uncertainty: the treatment effectiveness for AD and MCI patients, the risk of progression to AD for MCI patients at low risk, costs of formal care and informal care for patients with mild AD living in the community, and the probability of transition from community to nursing home for patients with mild AD. Among them, the main sources of uncertainty were the treatment effectiveness. Collecting data on the other 31 parameters has almost no additional benefit.

A future study in which gathering data on the treatment effectiveness of ChEIs for mild AD patients would have an optimal sample size of 1,700 with the expected benefit of \$29 million based on the estimation that about 10% newly diagnosed MCI patients would be affected by this decision question for 2 years. Furthermore, sensitivity analyses demonstrated that the result of the estimated optimal sample size remains robust with varying the study cost assumption. Additional research collecting information on treatment effectiveness of ChEIs for MCI patients would have an optimal sample size of 3,000.

It is known that considerable uncertainty is surrounding the treatment effectiveness for delaying the progression from MCI to AD and the progression among AD stages and thus many clinical trials are undertaken to obtain the better estimate of these parameters. By conducting a VOI analysis, we recognize the societal expected benefit of potential treatments on MCI patients to delay the AD progression. We then estimated the optimal sample size of a new study by maximizing these expected benefits. Methodological and computational challenges are the main reasons why a VOI analysis may not widely applied in real-life decision questions. Our study provides an example by thoroughly accounting for most relevant uncertainty pertaining to this decision problem and then presented the optimal sample size of a new study to collect more information before making a decision.

We acknowledge several limitations in this study. First, our decision model synthesizing evidences from various resources, were built based on several assumptions derived from the insufficient study results, such as the treatment efficacy for patients with mild AD or MCI patient, or treatment effect duration on MCI patients (the wide range of 95% CI). We may have overestimated the parameter uncertainty and in turn affected the results of VOI analysis. Second, we did not and were unable to account for all the potential uncertainty in this decision model, such as the type of model used (methodological uncertainty), and the applicability or generalizability of these results to a similar decision question. However, our analyses on uncertainty of parameters, structure (partially), and decision should have explored the most significant uncertainty that commonly appeared on the evaluation of the cost-effectiveness of a particular intervention. Finally, we used non-parametric GAM method proposed by Strong et al.,^{30,33} which was introduced in last two years, in this study due to the feasibility and the convenience. Further validation studies, especially the computation of the EVSI, will be beneficial to determine the applicability of this method in myriad of decision questions.

Several methods have also been proposed for conducting a VOI analysis,^{38,39} however, the results of which parameter generated the highest expected value should be indifferent even if they produce different value due to the method used. Future research of comparing different methods of conducting a VOI analysis may shed a light in the application of VOI analysis in a clinical problem.

4.5 Conclusion

Given our estimates of study costs, the efficient study design for the use of CSF biomarker testing on MCI patients for targeted early treatment involves a trial of 1,700 patients on treatment effectiveness for patients with mild AD and a trial of 3,000 patients on treatment effectiveness for MCI patients. VOI analysis provides value-based information in addition to the typical sensitivity analysis (deterministic or probabilistic) to examine the importance of input parameters. Moreover, VOI analysis may add some useful reference for policy makers, especially on the prioritization research projects based on their hypothetical societal benefit.

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Table 4.1 Characterization of input parameters for the early identification model.

Parameter	Mean	95% CI	Distribution	Source
Annual probability of progression from MCI to AD by CSF biomarker score				27
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)	
Annual transition probability^a				24,30
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)	0.11			44,45
Treatment effectiveness (RR)				
MCI patients	0.84	0.70-1.00	Lognormal(-0.17, 0.096)	20
AD patients)	35
mild to moderate	0.58	0.35-0.76	Lognormal(-0.55, 0.198)	
moderate to severe	0.95	0.64-1.41	Lognormal(-0.05, 0.114)	
Treatment harm				
Annual prob. of AE (control)	0.23	0.2-0.26	Beta(173.78, 581.77)	38
AEs in MCI (RR)	1.09	1.02-0.16	Lognormal(0.086, 0.02)	20
AEs in AD (RR)	2.51	2.14-2.95	Lognormal(0.92, 0.08)	37
Withdrawal due to AE ^b	0.19	0.14-0.24	Beta(41.67, 181.76)	37
Withdrawal due to non-AE	0.049	0.037-0.063	Beta(52.37, 1016.4)	Assumed
Health utility				
MCI	0.73	0.58-0.88	Beta(23.86, 8.82)	33,41
AD				
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 ^c	0.99	0.988-0.991	Beta(9800, 99)	Assumed, ⁴³

Table 4.1 Continued.

Parameter	Mean	95% CI	Distribution	Source
Cost (\$, per person-year)				
MCI	7,744	3,872-11,617	Gamma(15.36, 0.0020)	65
Formal ^d				55
Mild AD				
community	9,104	4,552-13,657	Gamma(15.36, 0.0017)	
nursing home	49,371	24,685-74,056	Gamma(15.37, 3.11)	
Moderate AD				
community	13,452	6,726-20,178	Gamma(15.36, 0.0011)	
nursing home	53,736	26,868-80,604	Gamma(15.37, 2.86)	
Severe AD				
community	20,276	10,138-30,414	Gamma(15.37, 7.58)	
nursing home	57,584	28,792-86,377	Gamma(15.37, 2.67)	
Informal ^e				55
Mild AD				
community	11,528	5,764-17,291	Gamma(15.36, 0.0013)	
nursing home	1,229	615-1,844	Gamma(15.32, 0.0125)	
Moderate AD				
community	19,955	9,978-29,933	Gamma(15.36, 7.70)	
nursing home	944	472-1,416	Gamma(15.34, 0.0163)	
Severe AD				
community	20,115	10,058-30,173	Gamma(15.37, 7.64)	
nursing home	998	499-1,497	Gamma(15.32, 0.0153)	
Drug (donepezil)	2,844	1,422-4,266	Gamma(15.35, 0.0054))	AWP, ⁶⁶
Office visit due to treatment (per time)	81	41-122	Gamma(14.88, 0.1837)	31
CSF biomarker testing (per person)	315	158-473	Gamma(15.50, 0.0492)	67

^aWe obtained the combined stage and nursing home transition probabilities by multiplying stage-to-stage and stage-to-nursing home transitions.

^bAnnual probability derived from 6-month data by the exponential function ($0.19=1-\exp[-0.1032*2]$).

^cIncorporated as disutility due to the treatment

^{d, e}Estimates from published studies.

Abbreviation: AD, Alzheimer's disease; MCI, mild cognitive impairment; RR, relative risk; AE, adverse event; AWP, average wholesale price; Com, community; NH, nursing home; CI, confidence interval.

Table 4.2 Cost-effectiveness results for CSF biomarker testing and treatment on patients with MCI.*

Strategy [§]	Cost (\$)	QALYs	ICER (\$/QALY) [¶]
Treat high or intermediate	265,211	7.487	
Treat high	265,445	7.499	Weakly dominated
MCI treatment	265,665	7.515	16,500
No MCI treatment	270,609	7.683	29,400
Treat low or intermediate	271,460	7.699	Weakly dominated
Treat low	271,694	7.710	39,500

*If MCI patients received treatment, no treatment was provided when they convert to AD.

[§]MCI treatment stands for treating all MCI patients, treat high was treating MCI patients at high risk, treat high or intermediate was treating MCI patients at high or intermediate risk, treat low was treating MCI patients at low risk, treat low or intermediate was treating MCI patients at low or intermediate risk, and no MCI treatment was no treatment on all MCI patients until they convert to AD (based on clinical expert opinion).

[¶]The value was rounded to the nearest \$100.

Abbreviation: CSF, cerebrospinal fluid; MCI, mild cognitive impairment; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

Table 4.3 Estimation of expected net benefit of sampling by the affected population and the study costs on the parameter of treatment effectiveness for patients with mild AD.

Affected population (thousand)*	Study cost					
	Mean		Lower		Upper	
	ENBS	Optimal n	ENBS	Optimal n	ENBS	Optimal n
Mean, 30,983	29,318,538	1,700	33,154,395	2,000	22,654,395	2,000
Lower, 23,391	20,492,803	1,700	24,172,855	2,000	13,672,855	2,000
Upper, 38,626	38,203,905	1,700	42,196,622	2,000	31,696,622	2,000

*The mean, lower bound and upper bound of the study cost were \$5 million, \$2.5 million, and \$10 million for the fixed cost and \$1,000, \$500, and \$2,000 for the varied cost per patient, respectively.

AD: Alzheimer's disease; ENBS: Expected net benefit of sampling. ENBS= population expected value of sampling information (EVSI) – study costs.

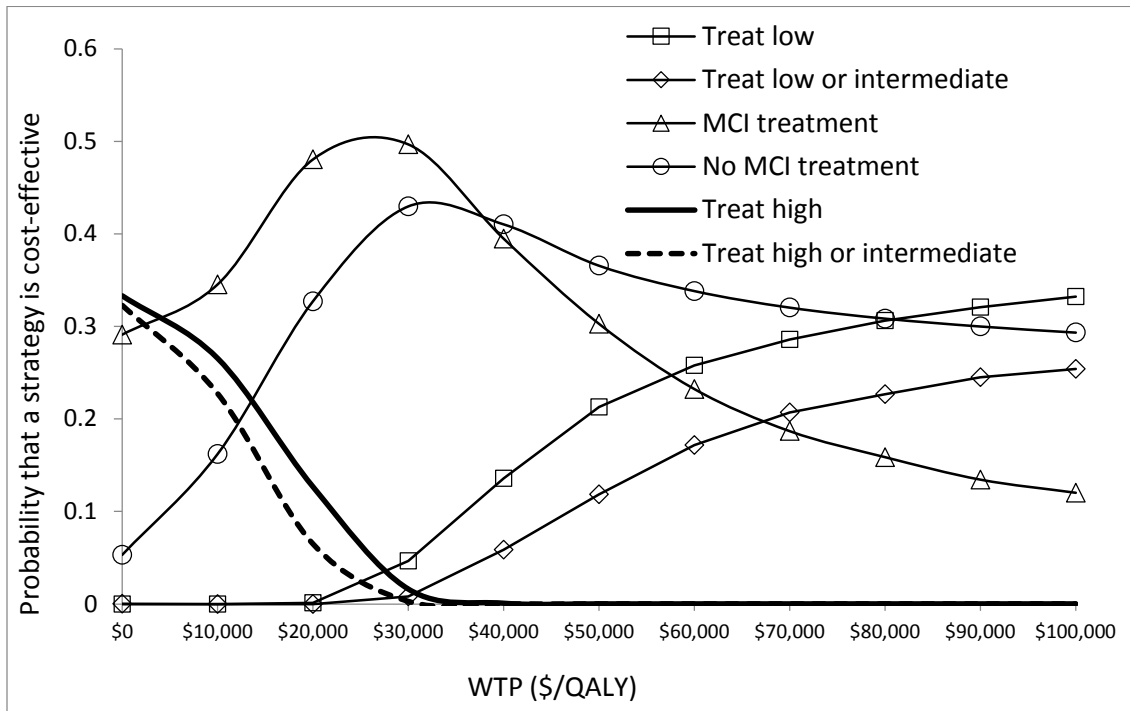


Figure 4.1 Cost-effectiveness acceptability curve showing the probability each strategy is optimal at various willingness to pay (WTP) thresholds given. The total probability adds to 1 for each WTP threshold.

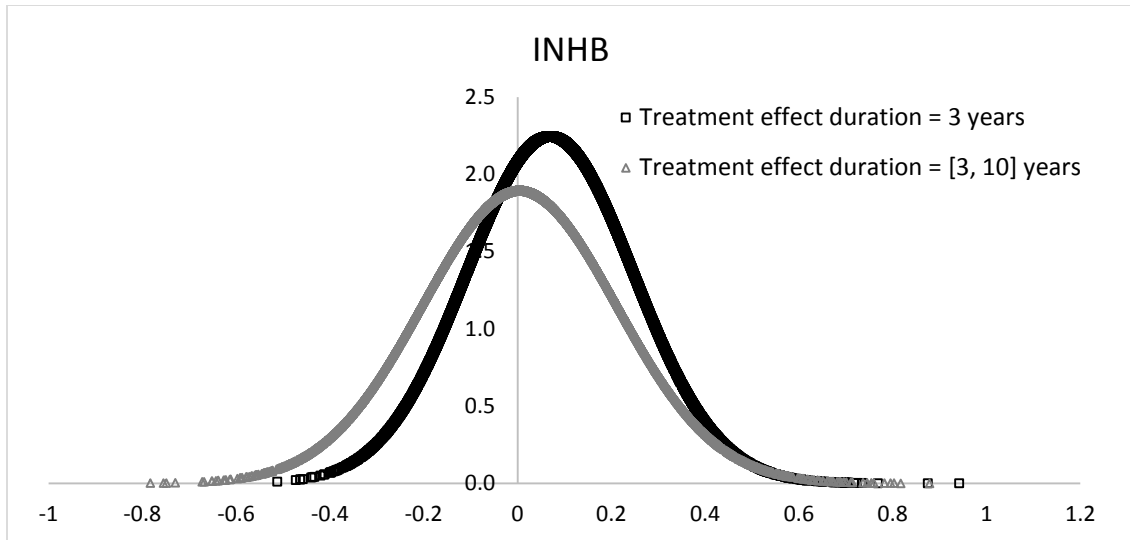


Figure 4.2 Comparison of the distributions of incremental net health benefit (INHB) of no MCI treatment vs. MCI treatment between treatment effect duration with 3-year and with varying from 3 to 10 years on MCI patients. MCI: mild cognitive impairment.

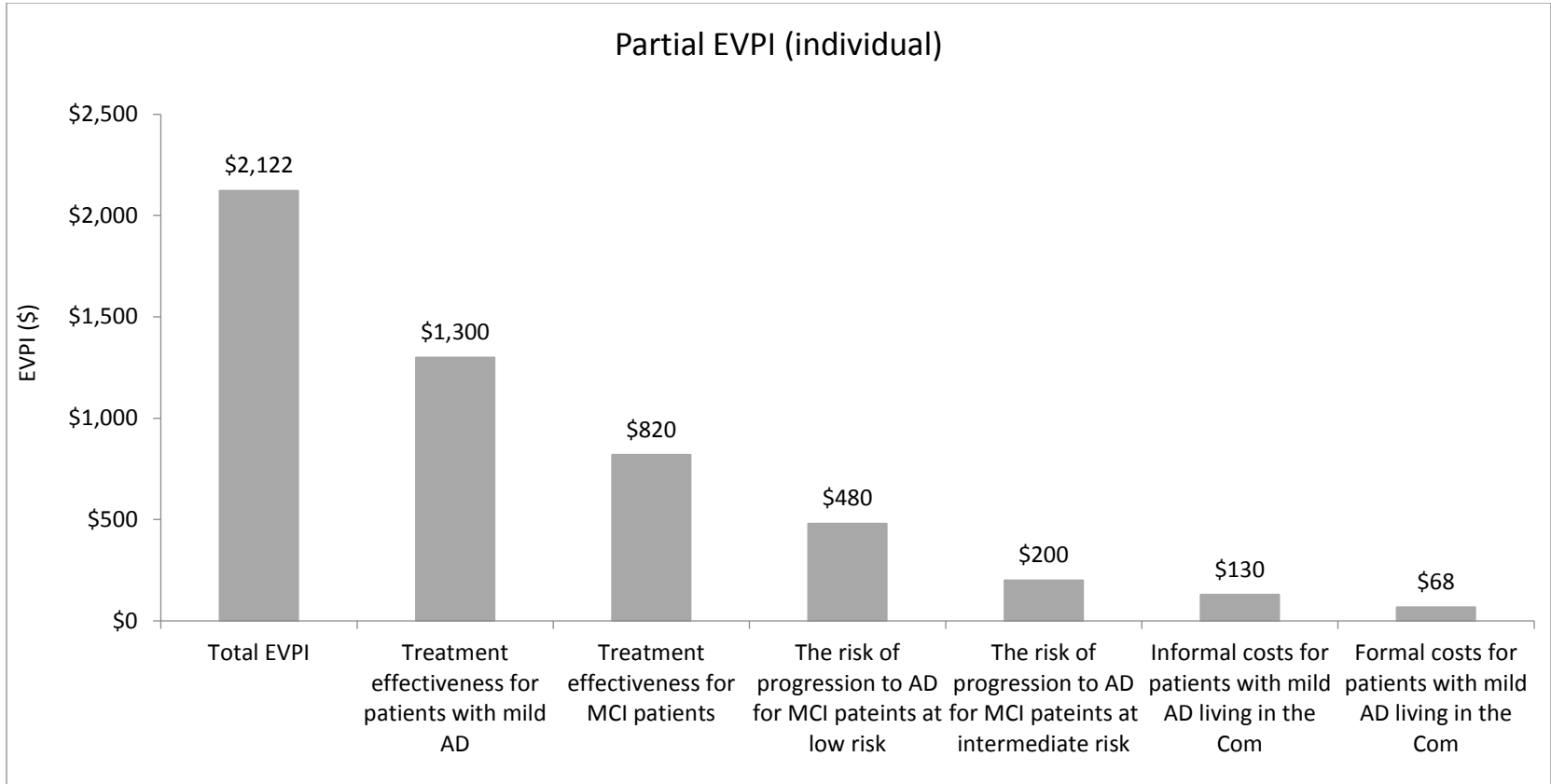


Figure 4.3 Partial expected value of perfect information (partial EVPI) for an individual parameter. AD: Alzheimer’s disease; MCI; mild cognitive impairment; Com: community.

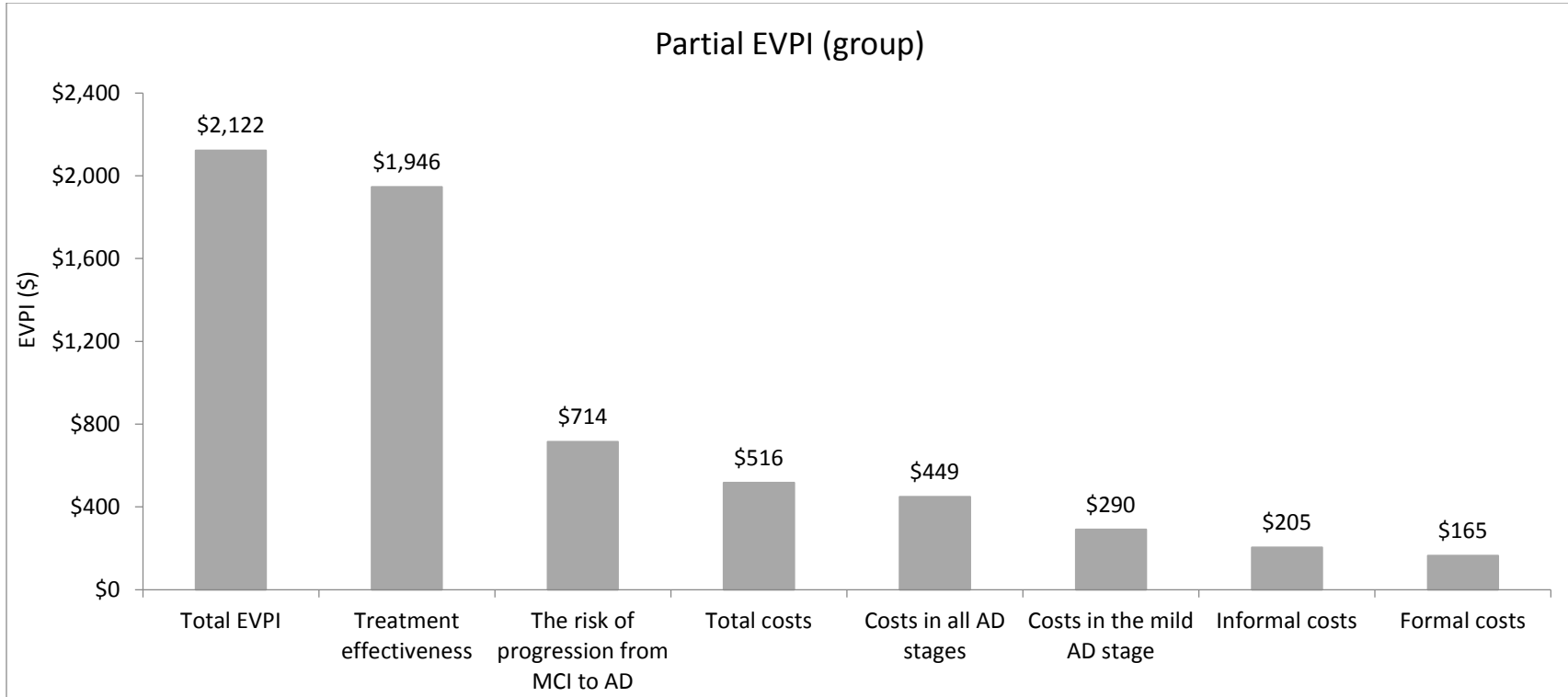


Figure 4.4 Partial expected value of perfect information (partial EVPI) for sets of parameters. AD: Alzheimer’s disease; MCI; mild cognitive impairment. Treatment effectiveness includes the treatment effect both on MCI patients and on patients with mild AD.

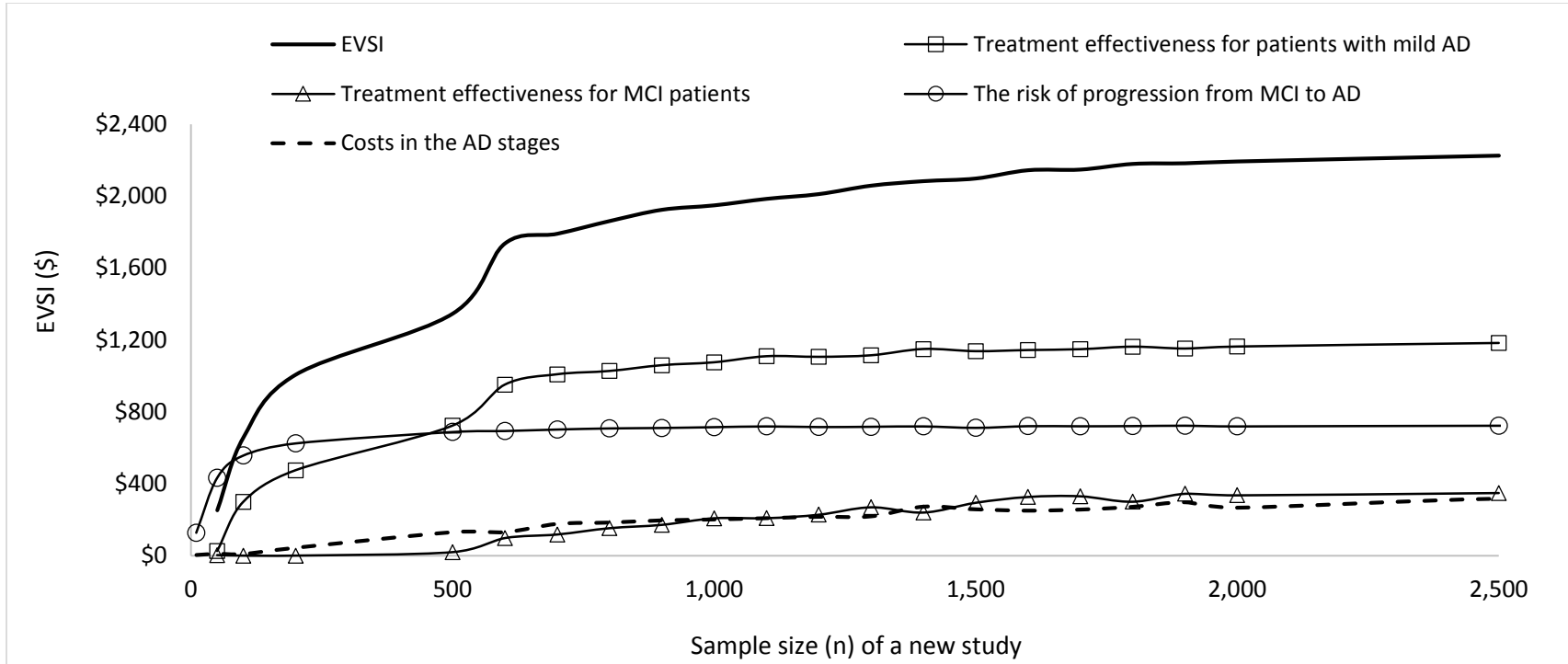


Figure 4.5 Partial expected value of sampling information (partial EVSI) by sets of parameters. AD: Alzheimer's disease; MCI; mild cognitive impairment.

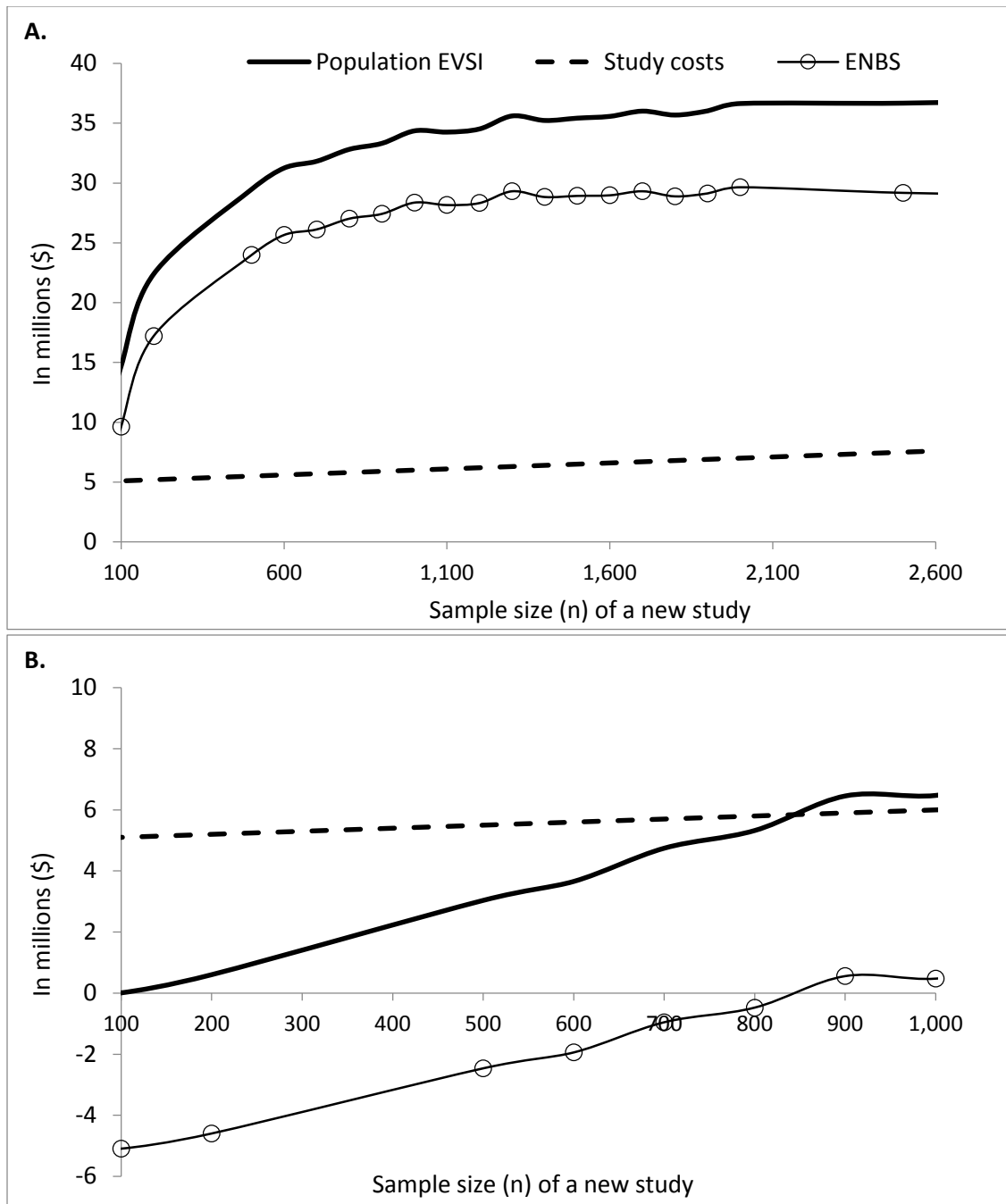
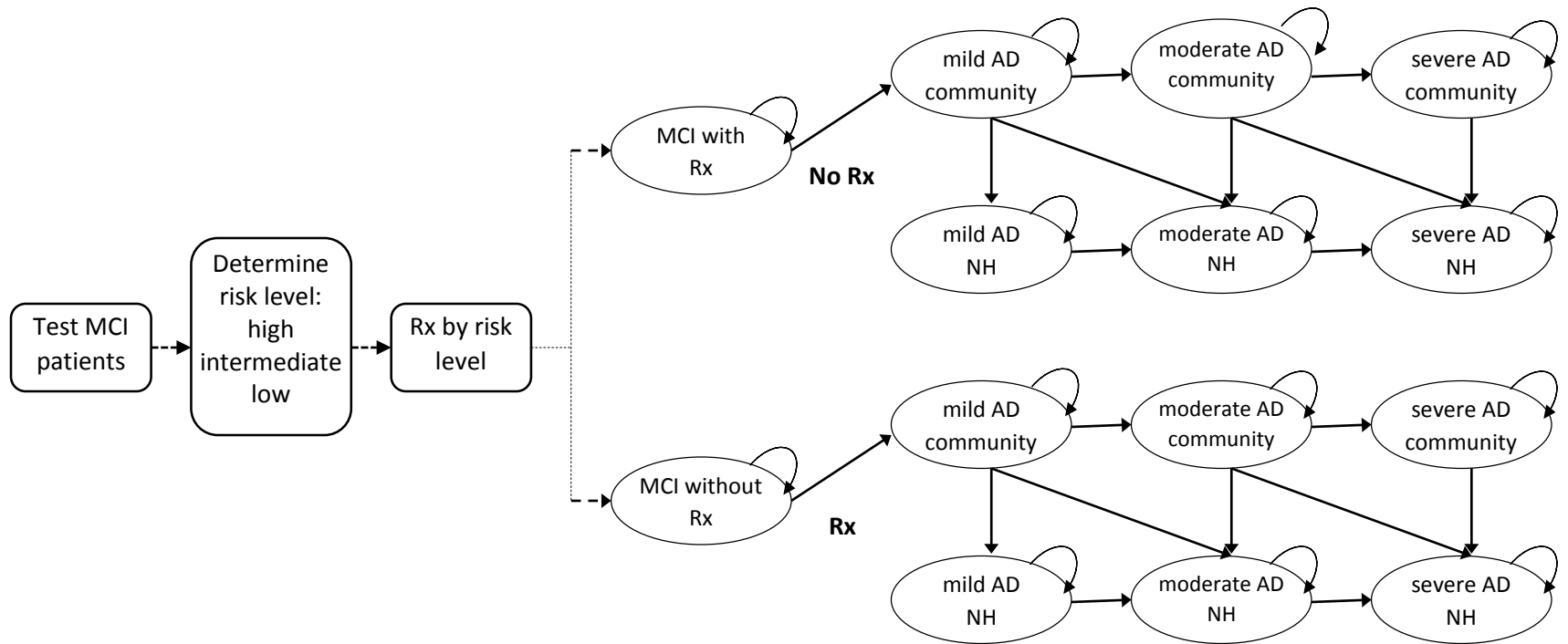


Figure 4.6 Population expected value of sample information (EVSI) for treatment effectiveness for patients with mild AD (Panel A) and treatment effectiveness for MCI patients with (Panel B), study costs, and expected net benefit of sampling (ENBS). ENBS= population EVSI – study costs. Study costs for an individual parameter are \$5 million of a fixed cost and \$1,000 per patient of a variable cost, respectively.

Appendix 4.A Schematic diagram of CSF biomarker testing and subsequent treatment on patients with MCI.



Appendix 4.B Illustration of expected value of perfection information (EVPI) calculation

In this simplified example, we modeled the expected value of outcomes (net monetary benefit, NMB) from our decision model based on only two strategies - treat all MCI patients (MCI treatment) or treat only when MCI patients convert to AD (no MCI treatment). We assumed two parameters of the risk of progression from MCI to AD (mean = 0.1; SD = 0.03) and treatment effectiveness for MCI patients (mean = 0.8; SD = 0.12). Both followed a beta distribution in the PSA. The table below represented the simulated output from ten iterations generating a NMB for each strategy. With current information (the risk of progression to from MCI AD and the treatment effectiveness), the best we can do is to choose the alternative with the highest expected NMB [$\max_d E_\theta \text{NMB}(d, \theta)$], which in this example is to choose treating all MCI patients with expected NMB with \$393,300 in this example. With perfect information (the resolution of uncertainty surrounding these two parameters), we could choose the strategy with the maximum benefit for each iteration [$\max_d \text{NMB}(d, \theta)$], this is, choose MCI treatment for iteration 1; no MCI treatment for iteration 2, no MCI treatment for iteration 3, and so on. However, we do not know in advance which of these estimates of input parameters will turn out to be true, so the expected NMB with perfect information is simply the expectation of the maximum NMB (\$404,800). The EVPI is then the difference between the expected NMB with the perfect information and with current information (\$404,800 - \$393,300 = \$11,500). This is equal to the average opportunity loss of making a wrong decision in the samples of the PSA output.⁵

Table. EVPI calculation algorithm: 10 iterations of second-order Monte Carlo simulation.

Iteration	P(AD)	Rx Effect	NMB (early Rx)	NMB (late Rx)	Sample best	Sample Max	Baseline Max	Opportunity loss
1	0.08	0.57	504,500	426,500	Treat	504,500	504,500	504,500-504,500 = 0
2	0.04	0.83	549,000	598,000	No treat	598,000	549,000	598,000-549,000 = 49,000
3	0.15	0.86	275,000	277,500	No treat	277,500	275,000	277,500-275,000 = 2,500
4	0.13	0.68	318,500	296,000	Treat	318,500	318,500	318,500-318,500 = 0
5	0.12	0.86	321,500	318,500	Treat	321,500	321,500	321,500-321,500 = 0
6	0.06	0.90	457,500	504,000	No treat	504,000	457,500	504,000-457,500 = 46,500
7	0.14	0.69	319,500	287,000	Treat	319,500	319,500	319,500-319,500 = 0
8	0.08	0.76	410,000	427,000	No treat	427,000	410,000	427,000-410,000 = 17,000
9	0.09	0.69	459,000	414,500	Treat	459,000	459,000	459,000-459,000 = 0
10	0.13	0.68	318,500	296,000	Treat	318,500	318,500	318,500-318,500 = 0
Average	0.10	0.75	393,300	384,500	60% early Rx	404,800	393,300	Overall EVPI = \$11,500
			$\max_d E_\theta \text{NMB}(d, \theta)$			$E_\theta \max_d \text{NMB}(d, \theta)$		

Note:

1. Net monetary benefit (NMB)= QALY \times λ – cost. λ is willingness to pay and is \$50,000/QALY.
2. Expected value of perfect information (EVPI) = $\frac{1}{N} \sum_{n=1}^N \max_d NMB(d, \theta^{(n)}) - \max_d \frac{1}{N} \sum_{n=1}^N NMB(d, \theta^{(n)}) = 11,500$.
3. E: expectation; θ : parameters of interest; d: treatment strategies (MCI treatment or no MCI treatment), which was 2 in this example; N: the number of iteration, which was 10 in this case; P(AD): the risk of progression from MCI to AD; Rx effect: treatment effectiveness for MCI patients.
4. Sample best, the strategy with the highest net benefit of the sample; Baseline Max, the outcome of the strategy with the overall optimal outcome; Sample Max, the outcome of the strategy with the highest net benefit of the sample; Treat, MCI treatment; No treat, no MCI treatment.

Chapter 5. Summary and Implications for Research and Policy

The objective of my thesis was to explore the potential of using cerebrospinal fluid (CSF) biomarker testing to target early treatment for patients with mild cognitive impairment (MCI) who are at risk of developing Alzheimer's disease (AD).

In paper 1, I examined whether or not CSF biomarker levels allow for risk stratification among MCI patients to identify those patients at higher risk of developing AD. I analyzed data on MCI patients from the Alzheimer's Disease Neuroimaging Initiative to estimate their risk of developing AD for up to 6 years on the basis of baseline CSF biomarkers. I used time-dependent receiver operating characteristic (ROC) analysis to identify the best combination of biomarkers to discriminate those who converted to AD from those who remained stable. I used these data to construct a multi-biomarker score and estimated the risk of progression to AD for each quintile of the multi-biomarker score. I found that $A\beta_{1-42}$ and P-tau_{181p} were the best combination among CSF biomarkers to predict the overall risk of developing AD among MCI patients (area under ROC curve= 0.77). The hazard ratio of developing AD among MCI patients with high-risk biomarker scores (the 3rd, 4th, and 5th quintiles) was about 4 times greater than MCI patients with low-risk scores (the 1st quintile) (95% confidence interval [CI], 1.93-7.26). The index developed in my thesis constitutes a reasonable measure with regard to the risk classification of MCI patients to target early interventions (such as potentially effective treatments or life management strategies), however, further validation studies should be applied on a population with relatively early stage of MCI to fully describe the continuum of CSF biomarker levels and the disease progression of MCI for better discriminatory performance if possible. Furthermore, cost-effectiveness of using biomarker testing combined with subsequent interventions could be performed to show the utility of our risk stratification approach to payers by targeting different intervention strategies based on the risk level determined by this index (with accurate diagnosis of MCI as the premise).

In Paper 2, I quantified the potential clinical value of CSF biomarker testing for patients with MCI. I developed a state-transition Markov model to project AD-free life years (i.e., average time to conversion to AD), quality-adjusted life years (QALYs), and lifetime costs. I conducted a cost-effectiveness analysis (CEA) on the use of CSF biomarker testing with cholinesterase inhibitor treatment for MCI patients to delay the clinical diagnosis of AD (test-treat) compared to no testing, including treating only when MCI patients convert to AD (no MCI treatment), and treating all MCI patients (MCI treatment). For the test-treat strategies, we considered treating different levels of risk using results from Paper 1- treating MCI patients at high risk or treating MCI patients at high or intermediate risk. CEA results indicated that no MCI treatment resulted in the highest cost and the highest effectiveness, with an incremental cost-effectiveness ratio of \$29,400 per QALY compared with MCI treatment. With accounting for uncertainty of all input parameters, PSA results showed that there was a 63% chance that no MCI treatment was cost-effective over a 37% chance of MCI treatment was preferred. In addition, it was shown that the MCI treatment strategy would produce greatest benefits if we allowed treatment initiated in both MCI and AD stages. This implied that an alternative treatment for patients with mild AD with the relative risk not greater than 0.66 (less effectiveness) and comparable to the current treatment on MCI patients, which allows for the continued treatments, would have the significant impact on the CEA results. Accordingly, it is of value to explore the possibility of treatment continuum from MCI to AD stages. Although the primary test-treat strategies were never found to be cost-effective, we found the strategy of treating MCI patients at low risk was cost-effective when targeting MCI patients at low risk in the post-hoc analysis. Based on the current evidence, this study demonstrates the potential for early-targeted interventions for MCI patients who are at risk of developing AD, especially for those at low risk.

In Paper 3, I estimated the expected value of reducing parameter uncertainty related to the decision whether or not to target early treatments on patients with MCI who are at risk of developing AD. Uncertainty surrounding the input parameters of the decision model constructed in Paper 2, including all six treatment strategies on MCI patients was assessed by value of information analyses (VOI) to estimate the potential benefits of gathering more information (through additional research) about the input parameters. The total expected value of perfect information (EVPI) of additional research of collecting data on all input parameters was \$2,122 per patient. The parameter of treatment effectiveness for patients with mild AD and treatment effectiveness for MCI patients were responsible for most of uncertainty (partial EVPI = \$1,300, and \$820, respectively). For illustrative purpose of how to use EVSI to estimate the optimal size of a new study, we demonstrated that new studies, given some assumptions on the study costs, in which collecting data on the parameter of treatment effectiveness for patients with mild AD would have an optimal sample size of 1,700 patients. A study collecting data on the treatment effectiveness for MCI patients would have an optimal sample size of 3,000 patients. Methodological and computational challenges are the main reasons why VOI analysis may not be widely applied in real-life decision problems. Several methods have been proposed for conducting VOI analysis, however, and future research of comparing different methods may shed light on how to apply VOI analysis to a clinical problem. Our study provided an example by thoroughly accounting for the most relevant uncertainty pertaining to a decision and also estimated the optimal size of a new study on a specific input parameter if the new study is justified. This would be informative in addition to the typical sensitivity analysis (deterministic or probabilistic). Moreover, VOI analysis may add some useful reference for policy makers, especially on the prioritization research projects based on their hypothetical societal benefit.

Overall, CSF biomarkers provide the potential of categorizing MCI patients into different risk levels of developing AD for targeted early interventions, although the risk levels of progression from MCI to AD was only significant in the high-risk group (not in the intermediate-risk group) compared to the low-risk group. Results showed that CSF biomarkers seems to add value to guide whether or not to target early treatments on MCI patients in a CEA framework, especially for those at low risk. With future additional research on the key parameter (treatment effectiveness for MCI patients and treatment effectiveness for patients mild AD), however, CEA might produce different results. Our model and the findings from our analyses could be used to guide further research evaluating the cost-effectiveness of other biomarkers used to target early treatment on MCI patients at risk of developing dementia.

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Chapter 1

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