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

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Abstract

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

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

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

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

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

1. Introduction

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

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

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

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

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

2. Methods

2.1. Design

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

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

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

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

2.2. Model structure

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

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

2.3. Model assumptions

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