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Featured Article

Alzheimer's disease Archimedes condition-event simulator: Development and validation

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Abstract

Introduction: Several advances have been made in Alzheimer's Disease (AD) modeling, however, there remains a need for a simulator that represents the full scope of disease progression and can be used to study new disease-modifying treatments for early-stage and even prodromal AD.
Methods: We developed AD Archimedes condition-event simulator, a patient-level simulator with a focus on simulating the effects of early interventions through changes in biomarkers of AD. The simulator incorporates interconnected predictive equations derived from longitudinal data sets.
Results: The results of external validations on AD Archimedes condition-event simulator showed that it provides reasonable estimates once compared to literature results on transition to dementia AD, institutionalization, and mortality. A case study comparing a disease-modifying treatment and a symptomatic treatment also showcases the benefits of early treatment.
Discussion: The AD Archimedes condition-event simulator is designed to perform economic evaluation on various interventions through close tracking of disease progression and the related clinical outcomes.

Keywords: Alzheimer's disease (AD); Prodromal AD; Disease-modifying treatments; Simulation; Cost-effectiveness analysis; Biomarkers; Predictive equations

1. Introduction

Quantifying the total value of an intervention requires an understanding of how its effects as measured in a clinical trial will translate to benefits for patients over relevant time horizons (often their remaining lifetimes) in a real-world setting. In many cases, it is necessary to use a mathematical framework—a model or simulation—to extrapolate from trial-reported outcomes to a real-world setting.

Many decision-analytic models have assessed the cost-effectiveness of treatments for Alzheimer's disease (AD) in the last two decades [1–6]. Among economic models published in the last decade on AD treatment, virtually all of them have focused on symptomatic treatments (particularly acetylcholinesterase inhibitors or memantine) for patients with mild to severe AD. Most previous studies conceptualized the course of the disease in terms of health states defined by levels of disease severity according to categories of cognitive function, dependency level, or based on patient's location of care or need for full-time care [6,7].

Several advances have been made in AD modeling in the recent years, such as including disease progression measures

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such as behavior, function, and dependence, modeling of disease progression as a continuous process rather than using discrete health states, and using individual patient simulation techniques [8,9]. However, there remains a need for a disease simulation approach that integrates all these advances and represents the full scope of disease progression from the evolution of biomarkers of AD to cognitive and functional decline. This need is particularly acute to understand the value of the disease-modifying treatments (DMTs) currently in development for early-stage and even prodromal AD [10].

This article describes the AD Archimedes condition-event simulator (ACE), an individual patient simulation developed to predict the trajectory of cognitive decline in different stages of AD and the impact of treatment on that decline. We discuss the clinical and health economic inputs used in the simulator and show the results of external validations against results reported in the literature along with a case study comparing a DMT and a symptomatic treatment on disease progression.

2. Methods

2.1. AD ACE overview

The AD ACE is a patient-level simulator that captures the pathophysiology and management of AD, with a focus on simulating the effects of disease modification and early intervention on disease progression. The simulator incorporates interconnected predictive equations that have been derived mainly from longitudinal data sets; these equations describe disease progression through the evolution of AD biomarkers and various relevant patient-level scales of cognition, behavior, function, and dependence. The AD ACE also fully considers interrelated clinical, epidemiologic, and economic outcomes. The design of the AD ACE was based on a systematic literature review of AD economic modeling [11], International Society of Pharmacoeconomics and Outcomes Research good modeling practice guidelines [12], and a review of ongoing clinical trials for both symptomatic and DMTs of AD.

Fig. 1 is an influence diagram outlining the key relationships in this simulator. The hierarchy of biomarkers preceding cognitive and behavioral decline reflects the description from Jack et al. [13] of the cascade of disease progression in AD; however, the relationships between the components were only included where sufficient statistical evidence was present. Similarly, the relationships between cognitive and behavioral decline and subsequent loss of function and independence reflect the modeling approach used in prior economic models of mild to moderate dementia/AD [9,14].

In the AD ACE, prediction of biomarker progression is mainly determined by the patient's characteristics (age, race, sex, education, apolipoprotein E4 [*APOE* ε4] level) and relevant biomarkers. Cognitive, behavioral, functional, and dependence scores are, in turn, predicted based on patient characteristics, biomarkers, and other cognitive, behavioral, and functional scale values. In particular, cognition

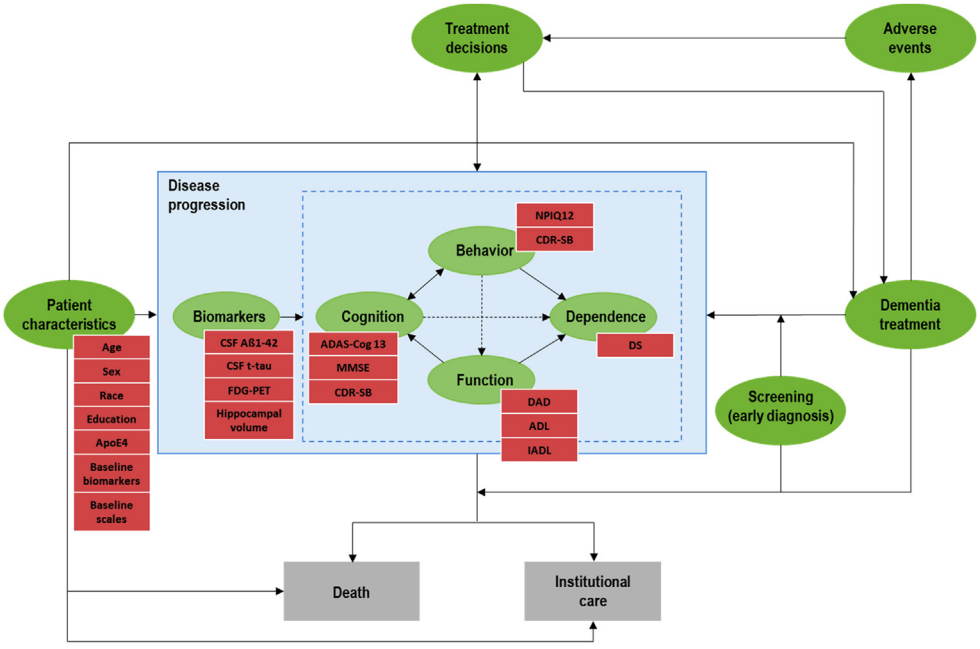

Fig. 1. Influence diagram outlining the key relationships in the AD ACE simulator. Abbreviations: ADAS-Cog13, Alzheimer's Disease Assessment Scale-Cognitive Subscale 13; ADL, Activities of Daily Living; *APOE* ε4, Apolipoprotein E4; CDR-SB, Clinical Dementia Rating Sum of Boxes; CSF Aβ1–42, Cerebrospinal Fluid β amyloid; CSF t-tau, Cerebrospinal Fluid total-tau; DAD, Disability Assessment scale for Dementia; DS, Dependence Scale; FDG-PET, Fluorodeoxyglucose–positron emission tomography; IADL, Instrumental Activities of Daily Living; MMSE, Mini-Mental State Examination; NPI-Q12, Neuropsychiatric Inventory Questionnaire 12.