Health economic modeling for Alzheimer’s disease: Expert perspectives

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Abstract: The successful development of an economic model for the evaluation of future Alzheimer’s disease (AD) interventions is critical to accurately inform policy makers and payers. As our understanding of AD expands, this becomes an increasingly complex and challenging goal. Advances in diagnostic techniques for AD and the prospect of disease-modifying treatments raise an urgent need to define specifications for future economic models and to ensure that the necessary data to populate them are available. This Perspective article provides expert opinions from health economists and governmental agency representatives on how future economic models for AD might be structured, validated, and reported. We aim to stimulate much-needed discussion about the detailed specification of future health economic models for AD.

KEYWORDS
Alzheimer’s disease, costs, dementia, disease-modifying treatment, economic models, model structure, pre-dementia, quality-adjusted life years, quality of life
1 | INTRODUCTION

Advances in diagnostic techniques for Alzheimer’s disease (AD) and the prospect of disease-modifying treatments (DMTs) could reduce the significant impact of AD on health and health systems globally. However, many health-care payers will critically review new technologies to formally assess their value for money, with decision-analytic modeling being a key methodology. Demonstrating value may be challenging as existing health economic models for AD have significant limitations, such as oversimplification of the natural history of the disease with the limited reflection of disease progression by cognition only in a small number of aggregated health states, lack of clarity about methodology and assumptions with substantial improvement required in terms of justification of key model components and data selection, heterogeneity between models in terms of the costs and outcomes included, and difficulties in extrapolating the treatment effect beyond the trial period, as highlighted by recent (systematic) reviews.1–5

It is therefore important to engage the AD research community, and in particular, clinical and epidemiological researchers conducting, designing, and interpreting studies who are in a strong position to improve the identified gaps in the literature, so that they better align their primary and secondary outcomes with the questions that reimbursement bodies are raising about the impact and value of interventions. As decision-making aids, health economic models must address the factors that are important to a particular decision, including treatment goals and available treatment options. Given the latest advances in terms of DMTs,6 models covering the full disease spectrum will be necessary to assess the value of these drugs.

- The pre-dementia stage needs to be reflected in future economic models.
- Disease-modifying therapies’ effectiveness will likely be measured with biomarker outcomes.
- It is recommended that models include the core domains of cognition, behavior, and function.
- A societal perspective should be the default due to the role of informal caregivers.
- Large and representative real-world data sets are needed to inform and validate models.

The ROADMAP (Real world Outcomes across the AD spectrum for better care: Multi-modal data Access) project was a pan-European effort involving representatives from academia, industry, and governmental and non-governmental organizations to develop a consensus on how to use real-world evidence (including economic data) relevant to AD.7 During this project we held several meetings with experts on AD health economic evaluation and modeling from a variety of backgrounds within and outside the ROADMAP consortium, representatives from health technology assessment (HTA) agencies, patient charity organizations, and patient and caregiver representatives. The purpose of these meetings was to discuss the best way of conducting economic evaluations of DMTs for AD and to identify pitfalls that, if not avoided, could undermine the acceptability of future models.

This Perspective article aims to stimulate much-needed discussion about the detailed specification of future health economic models for AD among a variety of stakeholders in the field. To start these discussions, we provide here statements of agreed viewpoint reached by a multidisciplinary team on how future economic models for AD might be structured, validated, and reported to improve the transparency of the process and make the results meaningful and reliable. These agreed viewpoints were reached through a deliberative process to gather expert opinions in the field of AD by means of:

- Telephone and face-to-face group discussion meetings with experts on health economic modeling within the ROADMAP consortium over the course of 1.5 years.
- Four telephone and face-to-face group discussion meetings with representatives from HTA agencies, patient charity organizations, and patient and caregiver representatives.
- One face-to-face group discussion meeting with international experts not involved in ROADMAP on AD health economic evaluation and modeling.

These meetings were moderated by ROADMAP participants and followed predefined discussion topics that drew on a set of internally developed systematic reviews, and had an open character (i.e., no Delphi methodology was applied). Recommendations from reviews of existing models were also collected. Details on the discussed topics in this process can be made available upon request.

All views were aggregated by selecting those that were mentioned multiple times or considered important by the authors, and then jointly reviewed to reach a consensus.

RESEARCH IN CONTEXT

1. Systematic review: The authors systematically reviewed the literature on economic models for Alzheimer’s disease (AD) and used the findings to elaborate questions for discussion with experts in the field.
2. Interpretation: Future models will be expected to reflect interventions targeting pre-dementia and include at least the three core domains of AD. The effectiveness of disease modifying treatments will likely be measured using cognitive assessments, global clinical measures or biomarker outcomes depending on whether patients show initial symptoms of impairment. Biomarkers will also be used to select treatment eligible populations. Models will therefore require a working representation of the pathological cascade. A societal perspective should be the default given the importance of informal carers.
3. Future directions: Additional data is necessary on costs and quality-adjusted life years in pre-dementia, on the nature and pace of disease progression from pre-dementia to dementia, and on the long-term costs and benefits of early detection and treatment.
2 | DIAGNOSIS

From a health economic perspective, the availability, performance, and cost of diagnostic tests for AD will have a direct bearing on how accurately and at what cost the optimal target population to be treated can be identified. The selection of patients for a DMT could be highly specific to a particular biomarker or be based on more general risk factors or biological determinants. In either case, the diagnostic pathway is likely to be an intrinsic part of the economic evaluation of the DMT, as it will have an effect on costs and cost-effectiveness. Health economic models should therefore integrate the diagnostic pathway, including information on test performance and costs, to accurately estimate the costs and health benefits of a DMT and to optimize the selection of patients. Further, the consequences of such testing (including the impact of false positives and false negatives) would have to be included in the economic analysis of the use of the DMT.

3 | THE PROGRESSION OF ALZHEIMER’S DISEASE

Although patients typically show biomarkers of the pathology before they show symptoms of cognitive, neuropsychiatric, or behavioral decline, these pathological features are typically not part of current dementia stage–oriented economic models.

It may likely be important to reflect the pathological hallmarks in future health economic models because DMT effectiveness is potentially expressed using biomarker outcomes that can serve as measures of disease progression in the absence or minimal presence of symptoms in pre-dementia stages of AD.

4 | MODEL STRUCTURE

Ideally, AD models should address at least three core domains: cognition, function, and behavior, all of which are associated with the health-related quality of life (HR-QoL) of patients and caregivers and are also associated with costs of caregiving. A multidomain approach might detect (subtle) domain-specific changes that are missed in a single-domain model (e.g., functional changes in the early stages of the disease). Changes in cognition, function, or behavior can lead to dependency and institutionalization. However, there is disagreement concerning whether dependency and institutionalization can be generalizable core domains in economic models, as the rules for determining the level of dependency, and consequently financial support, vary between countries, as do rates of institutionalization. Advances in diagnostics may make it possible to address AD symptoms and progression from a biological perspective. But until longitudinal data on biomarkers are available, predictions of cognition, function, and behavior will have to be based on time and previous symptoms.

Different modeling approaches may be needed for different parts of disease progression (e.g., a decision tree-based approach for the diagnostic phase, followed by a Markov or semi-Markov approach).

Where clinical trials have used surrogate measures such as biomarker changes as primary outcomes, a model would require plausible evidence to support the link between these surrogate outcomes and final endpoints, and thereby enable extrapolation of trial outcomes to long-term disease progression and its associated costs and quality-adjusted life years (QALYs).

5 | PATIENT CHARACTERISTICS

While the field is evolving in the understanding of how patient characteristics may influence disease progression and prognosis, it is recommended that key factors known at the time of model development should be included, such as age, gender, biomarker profile, genotype, symptom status, and comorbidities defined according to some combination of the core domains discussed previously (cognition, functional ability, and behavior).

6 | PERSPECTIVE

Many economic models estimate costs from the perspective of the health-care system. However, AD causes a substantial economic and health burden across a much wider spectrum of society. Many of the services required by people with AD, particularly in the later stages of the disease, are not within the health-care sector (e.g., long-term care facilities). Additionally, much of the care for AD patients is provided by unpaid caregivers, including spouses and adult children. Caregivers of employment age may have to change their formal employment, and their caregiving responsibilities may lead to absenteeism or reduced work performance (presenteeism). And even though many carers will be retired, there are opportunity costs associated with foregoing other valuable activities to devote time to caregiving. Caring for someone with AD can also have significant health consequences; thus, caregivers’ health status and consumption of health-care resources may also have to be reflected. The impact of AD on caregivers will differ from country to country depending on available resources. Given these pervasive effects on multiple sectors, economic models of AD should use, or provide the option to use, a societal perspective.

Despite varying HTA requirements, all of the HTA agencies’ representatives felt that the caregivers’ perspective is important. However, whereas there was consensus that the caregiver’s own HR-QoL should be captured and included where possible, they had differing views on whether productivity loss and informal care costs should be included. It was agreed that the model should be capable of taking into account a broad range of costs and outcomes, ideally taking the full societal perspective, including capturing how the caregiver’s role evolves with disease progression in terms of costs and HR-QoL, but with the facility to aggregate or disaggregate these elements as required or present them in sensitivity analyses. This could be achieved by the dashboard of outcomes approach as one way to make transparent the effect of the different valuation options (or sensitivity analysis).

Different outcomes are expected for paid and unpaid caregivers.
7 | OUTCOMES AND OUTCOME MEASURES

At present, there is widespread heterogeneity in outcomes used in AD research. Cognitive impairment is a core defining feature of AD and is commonly included in health economic models. However, progressive cognitive decline is associated with functional decline, which includes impaired ability to carry out activities of daily living (ADLs). Functional decline is also determined by the patient’s social and family environment, as well as the pre-morbid functional level and co-morbidities. Although the natural history of functional decline in AD is still a topic of research, the functional decline is also a predictor of nursing home admission. Similarly, behavioral changes as AD progresses are independent predictors of resource use, including key transitions such as institutionalization. Combining these three domains might prove challenging as they are usually measured with different scales. Some experts have proposed a role for the level of dependency in modeling disease progression and its associated costs and HR-QoL changes. The level of dependency will influence the level of resources used and affect HR-QoL. It could therefore be an alternative approach to measuring disease progression and give payers a direct way of relating disease progression to resource requirements. However, dependency is an intermediate concept between clinical outcomes and care requirements and may therefore be less generalizable between countries or health systems than other measures of disease progression.

Decision makers may value some combination of function and behavior, as well as cognition, in health economic models for AD. Other measures such as dependency could also be important. Researchers should develop new data sources to elucidate how these measures interact and influence health outcomes and resource use.

A core set of outcomes (COS) would be desirable and ROADMAP has been working with stakeholders to identify a priority set of relevant outcomes. However, more research is required to produce a clear and standardized COS across all AD interventions, and all disease severity stages. Meanwhile, validation of mapping algorithms to permit analysts to construct bridges between different outcome measures will also facilitate a move toward a more consistent set of outcome measures.

7.1 | Costs

A model for AD should be able to consider different types of costs, depending on the perspective (e.g., payer or societal) and the decision makers’ requirements. It would be useful to incorporate caregiver time, for example, as a tangible monetized value that might be used in addition to the traditional direct medical care and institutionalization costs. It would also be important to understand on which budget different costs fall: for instance, the portion of direct costs which are met by out-of-pocket payments by people with AD or their families.

Current interventions with DMTs focus on pre-dementia, where there is little evidence on costs and HR-QoL. Gathering such evidence on costs for pre-clinical and prodromal AD should become a key research priority.

Spill-over effects (the effects that health conditions and services affecting one person can have on the physical and mental health of others) will also affect cost-effectiveness ratios in AD and could result in a re-ranking or re-ordering of priorities for decision makers.

7.2 | Quality of life

Many studies have used utility-based instruments such as the EQ-5D to assess HR-QoL in people across the spectrum of AD. However, such studies show discordance between self- and proxy ratings: caregivers report a pronounced decline in the patient’s HR-QoL as the disease progresses, whereas patients’ self-assessed HR-QoL displays much less decline with disease progression. This raises complex practical, policy, and ethical issues, which cannot easily be resolved. Clearly, models must be flexible enough to accommodate different options and scenarios. It could be important to incorporate a caregiver dimension in an AD model because caregiver-related variables may be important predictors of patient resource use and outcomes (e.g., time to institutionalization). Additionally, caregivers may exert an important influence on the patient’s HR-QoL. Finally, caregivers’ HR-QoL is affected by caring, particularly in later stages of AD, and influenced by patient comorbidities, especially depression and polypharmacy.

7.3 | Life expectancy

AD shortens life on average by 3 to 4 years. Understanding the impact of future treatments on life expectancy is critical. It is also important to know whether these new treatments prolong the early or late stages of the disease, as this could have radically different implications. Delaying symptom onset might extend the best part of a patient’s life. In contrast, prolonging life in the later stages of AD, when HR-QoL is low and costs are high, may be difficult to justify ethically and economically.

Drivers of mortality among AD patients are poorly understood. Multiple factors could contribute to increased mortality among AD patients. Also, the exact cause of death in an AD patient can be hard to ascertain and may be poorly recorded. Thus, it is uncertain whether a delay in AD progression would translate into increased survival. Hence, the way in which mortality is handled in a model requires careful consideration. The most common approaches are either a flat rate for mortality or mortality driven by disease stage measured in terms of cognitive function, in which mortality risk is stage dependent and assumes that those in the mild stage will have lower mortality age than those with severe disease, for instance. Other approaches include specifying mortality to be driven by age, independently of disease stage. Few models combine age- and severity-specific mortality, which would be our recommendation.
DATA SOURCES

AD takes decades to run its course, whereas AD clinical trials last only a few years. Consequently, economic modeling will have to make substantial use of data collected outside clinical trials (e.g., in observational studies, patient registries, electronic health records, and surveys). Ideally, these should be large and representative data sets with baseline information on deep phenotyping and biomarkers, repeated measures, and low attrition, as high attrition could be associated with severe dementia, resulting in a biased reflection of natural progression in late-stage disease. It will also be important to have the possibility of linking these data to trial endpoints.

UNCERTAINTY

Uncertainty in AD modeling presents itself as a double cone: large at the beginning (regarding disease onset, treatment effectiveness, and subject selection) and large at the end (regarding extrapolation to the effect of treatment on late-stage progression, institutionalization, and mortality). One solution is to conduct an extensive sensitivity analysis. Sensitivity analysis is critical in AD modeling, given the slowly progressive nature of the disease, the short duration (e.g., 18 months to 2 years) of clinical trials, and the consequent substantial uncertainty in how to extrapolate from clinical trial data.

MODEL VALIDATION

The biggest challenge will be in establishing external validity by comparing model predictions with independent data sources (e.g., clinical trials or observational data). Obstacles to external validations include the fact that candidate data sets may be poorly matched in population characteristics, might not record information in similar ways or intervals, may use different scales and instruments, and may be restrictive in providing access to patient-level data or otherwise facilitating such studies.

CONCLUSION: FUTURE CHALLENGES

We have identified the following as the main AD-specific health economic modeling challenges:

- The shift toward targeting the pre-dementia stage needs to be reflected in future models, but currently there is limited evidence on costs/QALYs in pre-dementia, on the nature and pace of disease progression from pre-dementia to diagnosis, or on the long-term costs and benefits of early detection and treatment.
- DMT effectiveness will likely be measured with biomarker outcomes that can represent natural disease progression in the absence or minimal presence of symptoms in pre-dementia stages of AD. Such biomarkers will also be used to select treatment-eligible populations. Future models will therefore require a working representation of the pathological cascade.
- Because of the heterogeneous presentation of AD and the range of views on how disease progression should be represented, future models will probably need to include at least the three core domains of cognition, behavior, and function—either directly or through other measures such as dependency.
- Informal caregivers play an important role in AD, incurring costs and HR-QoL changes as well as influencing these outcomes for patients. Because these outcomes cannot be ignored in modeling disease progression, a societal perspective should be the default. The likely need for models to extrapolate from biomarkers to disease progression over a lifetime will pose particular challenges in propagating parameter and model uncertainty.
- Model validation will also be challenging and will require large and representative real-world data sets with information on phenotyping and biomarkers, repeated measures, ascertainment of relevant outcomes, and low attrition.

DMTs for AD are now a reality and there is the urgent necessity to define specifications for future models and to ensure that the necessary data to populate them are available. We have presented some recommendations to address these gaps in the literature, but progress will require the involvement of experts from different fields working on AD. We, therefore, invite the research community, particularly researchers working on AD modeling, to respond to and comment on these recommendations.

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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