RTI (h)(s) Health Solutions

41141

Persistent Challenges in Alzheimer's Disease Modeling: Pragmatic Solutions to Inform the Road Forward

William L Herring, Josephine Mauskopf

RTI Health Solutions, Research Triangle Park, NC, United States

BACKGROUND

- As potential disease-modifying therapies (DMTs) for Alzheimer's disease (AD) approach the market, economic models will play an important role in helping decision makers assess the value for money and affordability of these innovations.
- The credibility of economic evaluations of these emerging AD therapies will depend on addressing structural and data challenges with transparent and evidence-based approaches.
- The development of biomarker-based diagnostic criteria for AD[1] and the current emphasis of DMT development efforts on patients in the predementia stages of AD[2] have the potential to exacerbate these challenges.

OBJECTIVE

- The objective of this study is to describe persistent methodological challenges recurring throughout the AD economic modeling literature and recommend practical solutions for future researchers.

METHODS

- Systematic literature reviews (SLRs) of economic models for AD published were identified through a targeted search of the published literature since 2010.
- A representative selection of published economic models for AD was extracted from the reference lists of the SLRs and supplemented with a targeted search for recently published models.
- The findings and recommendations from the SLRs were synthesized and used to identify recurring structural and data challenges; recently published models reflecting state-of-the-art approaches were reviewed to determine the extent to which these challenges persist.
- Trends in the evolution of modeling approaches across the selected economic models were synthesized to provide additional context for these recurring and persistent challenges.
- Finally, we compiled a list of pragmatic recommendations for addressing these challenges, taking into account the increasing availability of longitudinal, observational data; the anticipated limitations of clinical trial for DMTs at the time of launch; and established health technology assessment requirements.

RESULTS

- Our synthesis of five SLRs from the past decade[3-7] identified the following key findings and recommendations for economic models in AD:
  - Cognition alone is insufficient to reflect the complexity of AD symptoms and progression; multivariable approaches are needed.
  - Studying the full AD continuum requires bridging longitudinal data across cohorts while accounting for different instruments at different stages.
  - The testing and diagnostic process for patients with AD must be modeled explicitly, especially for evaluations of early interventions for predementia AD.
  - Greater transparency is required on model conceptualization, structural assumptions, data sources, and validation.
  - Models for hypothetical DMTs continue to vary widely in design and in their assumptions about long-term effectiveness, institutionalization, and mortality.
- The models selected from these SLRs and from the recent literature highlight the evolution of AD modeling approaches:
  - The approaches can be broadly categorized by how disease progression was modeled:
    - Continuous symptom measure (e.g., cognition) for an average patient (statistical regression models)[8-9]
    - Time to event (e.g., institutionalization) for an average patient (statistical time-to-event models)[10-11]
    - Continuous symptom measures for a sample of patients (patient-level simulations)[12-15]
    - Discrete severity levels for a cohort of patients (Markov-based models)[16-22]
  - Institutionalization (or the need for full-time care) was typically treated as a distinct health state in statistical time-to-event models and Markov models while being represented as a proportion of patients tied to symptom levels in patient-level simulation models.
  - Early models used to evaluate symptomatic AD treatments were appropriately focused on patients with AD dementia, while more recent models developed in anticipation of emerging DMTs have consistently included mild cognitive impairment due to AD and the asymptomatic stages of AD.
  - The inclusion of biomarker criteria and the diagnostic process for population identification became more common as models began to include predementia AD stages; however, it was relatively less common for models to use progression data specifically for biomarker-positive patients or to track biomarker progression over time.

Table 1. Fundamental Challenges for AD Modeling

Challenges	Context From Selected Published Models
1. Quantifying heterogeneity in population characteristics and the natural history of disease progression and dementia onset	• Varying rates of AD progression were observed across commonly used longitudinal data sets (e.g., ADNI, NACC, SveDem), potentially owing to differences in their population characteristics, applications of biomarker criteria, and approaches to AD staging • While biomarker data are increasingly available in longitudinal data sets, the natural history disease-progression data used in published models are not always specific to biomarker-positive patients
2. Assembling evidence supporting the extrapolation of short-term trial endpoints to long-term benefits	• Models for hypothetical DMTs in predementia AD assume long-term reductions in AD progression, which translate to delays in dementia onset and institutionalization • Relevant clinical measures in later disease stages may not be sufficiently sensitive to detect treatment effect in earlier disease stages, motivating a range of composite clinical endpoints • Biomarker endpoints reflecting the mechanisms of action for DMTs in development are not typically included in economic models, and their correlation with clinically relevant endpoints across the AD continuum has yet to be established • Clinical trial durations may be too short to fully establish the link between primary endpoints and long-term delays in progression
3. Addressing data gaps in costs, utilities, and mortality by disease severity accounting for age	• Older studies on costs, utilities, and mortality used in AD models largely focused on the dementia stages of AD • More recent cost and utility studies focusing on the predementia or mild dementia stages have not consistently included more advanced AD stages • Few cost, utility, or mortality studies have used biomarker criteria to align their populations with the populations targeted by DMTs in development • Models using continuous disease measures, including symptoms and biomarkers, need to map these measures to discrete health states to allow the use of published cost and utility data • Few models adjust for the role of increasing age in observed differences in costs and utilities across AD severity levels
4. Bridging differences in population, clinical and biomarker measures, and care settings across data sets and markets	• Data sources are often combined in models to obtain cost and utility parameters spanning the AD continuum despite potential differences in study populations and in AD diagnostic and staging criteria • Differences in local diagnostic and care patterns for AD, including institutionalization, are expected across markets where DMTs will be evaluated • In addition, local cost, utility, and mortality studies may vary in the clinical measures and cutoffs used to determine AD severity levels

ADNI = Alzheimer's Disease Neuroimaging Initiative; NACC = National Alzheimer's Coordinating Center; SveDem = Swedish Dementia Registry.

- Building on these insights, we identified four fundamental challenges for economic models being developed to evaluate emerging AD therapies (Table 1).
- Additional context from the selected published models specific to each of these challenges is summarized in Table 1.
- Based on the increasing availability of longitudinal data sources (e.g., NACC, ADNI, SveDem), the growing consensus around biomarker-based AD diagnosis, and the anticipated target populations and trial endpoints for DMTs in development for AD, we have identified the recommendations shown in Table 2.

Table 2. Recommendations for Addressing AD Modeling Challenges

Recommendations	Relevance to Challenges 1	2	3	4
Analyses comparing existing longitudinal data sets (including clinical trials, when available) should be conducted to better understand differences in population characteristics and risk factors within and between data sets; these analyses should be matched on patient characteristics, diagnostic and staging criteria, and progression endpoints where possible.	☑			☑
Existing longitudinal data sets also can be used to generate evidence of correlation between short-term clinical trial endpoints and long-term progression in support of treatment effect extrapolations.		☑		
Long-term follow-up of clinical trial participants should be planned to validate findings from these new analyses of existing longitudinal data sets.			☑	
Previously collected data on costs, utilities, and mortality, especially those including a proportion of patients with non-AD dementia, could be reanalyzed to isolate AD-specific estimates across disease severity levels, accounting for biomarker positivity when possible and for the impact of aging.	☑		☑	☑
Crosswalks between symptom measures (e.g., alternative cognitive or functional scales) and biomarker criteria (e.g., cerebrospinal fluid vs. positron emission tomography testing), including differences in how they are implemented across study populations, should be created to inform the appropriateness of combining data from multiple data sources and to support the adaption of economic models to local markets.	☑	☑		☑
Finally, economic models for AD should be developed with flexibility in their structural assumptions and in their ability to handle a diversity of data formats to facilitate local adaptations and to demonstrate the uncertainty in results attributable to both structural and input parameter uncertainty.	☑	☑	☑	☑

CONCLUSIONS

- Pragmatic solutions tailored to the available data and the anticipated profiles of DMTs in late-stage development should be pursued to support decision makers evaluating these therapies.
- The findings from these recommended studies and their impact on clinical and economic modeling outcomes can be used to further inform the design of long-term evidence-generation efforts once these DMTs are being used in real-world settings.

REFERENCES

1. Jack CR, et al. Alzheimers Dement. 2018;14(4):535-62.
2. Cummings J, et al. Alzheimers Dement (N Y). 2019;5:272-93.
3. Green C, et al. Value Health. 2011;14(5):621-30.
4. Handels RL, et al. Alzheimers Dement. 2014;10(2):225-37.
5. Hernandez L, et al. Pharmacoeconomics. 2016;34(7):681-707.
6. Gustavsson A, et al. Alzheimers Dement. 2017;13(3):312-21.
7. Mauskopf J, et al. Value Health. 2019;22:S272.
8. Fenn P, Gray A. Pharmacoeconomics. 1999;16(2):165-74.
9. Hauber AB, et al. Pharmacoeconomics. 2000 Apr;17(4):351-60.
10. Caro J, et al.; for the AHEAD Study Group. Neurology. 2001;57(6):972-8.
11. Bond M, et al. Health Technol Assess. 2012;16(21):1-470.
12. Weycker D, et al. Curr Med Res Opin. 2007;23(5):1187-97.
13. Getsios D, et al. Pharmacoeconomics. 2010;28(5):411-27.
14. Handels RL, et al. Alzheimers Dement. 2015;11(8):896-905.
15. Kansal AR, et al.; for the ADNI Collaboration. Alzheimers Dement (NY). 2018;16(4):76-88.
16. Neumann PJ, et al. Neurology. 1999;52(6):1138-45.
17. Jönsson L, et al. Pharmacoeconomics. 1999;16(4):409-16.
18. Budd D, et al. Clinicoecon Outcomes Res. 2011;3:189-95.
19. Sköldunger A, et al. Curr Alzheimer Res. 2013;10(2):207-16.
20. Anderson R, et al. Economic modelling of disease-modifying therapies in Alzheimer's disease. Personal Social Services Research Unit. 2018. Available at: www.lse.ac.uk/pssru.
21. Wimo A, et al. J Alz Disease. 2020;75(3):891-902.
22. Green C, et al. Alzheimers Dement. 2019. 15(10):1309-21.

CONTACT INFORMATION

William L Herring, PhD
Senior Director, Health Economics

RTI Health Solutions
3040 East Cornwallis Road
Post Office Box 12194

Research Triangle Park, NC 27709-2194
Phone: +1.919.541.6423
Fax: +1.919.541.7222
E-mail: wherring@rti.org

Presented at: Alzheimer's Association International Conference 2020; July 27-31, 2020; Amsterdam, The Netherlands