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Refining clinical trials for dementia prevention

Using a novel clinical prediction algorithm to enhance clinical trials in Alzheimer's disease

Yaakov Stern[1] | Eric Stallard[2]

[1] Columbia University, New York, NY, USA

[2] Duke University, Durham, NC, USA

Correspondence
Yaakov Stern, Columbia University, New York, NY, USA.
Email: ys11@cumc.columbia.edu

Abstract

Background: The course of Alzheimer's disease (AD) is heterogenous, in part because of individual heterogeneity in the disease's underlying biological changes. This heterogeneity can influence the efficacy and interpretation of clinical trials. We developed a Grade of Membershp (GoM) prediction model that can accurately predict time to important disease endpoints in individual patients. Here we present the model and discuss its implications for clinical trials in AD.

Method: The GoM model was developed in the Predictors 2 cohort. It incorporates 73 time-varying categorical covariates spanning 11 measurement domains including cognition, function; psychiatric symptoms, motor signs/symptoms and APOE genotype. We then tested the model in the separate Predictors 1 data set, consisting of 252 patients with mild AD at first visit who were followed semi-annually for up to 10 years. We applied the GoM model to data from each patient's first visit, which generates a baseline GoM status. We then generated predicted survival functions and used life table analyses to compare predicted and actual survival.

Result: The figure summarizes the actual survival curve for all patients, and the survival curves as predicted from the GoM model. The predictions fell well within the confidence intervals around the actual survival curve. We also divided the estimated survival into quintiles, and compared the predicted versus actual quintile-specific survival curves. Again, the predictions generally fell well within the confidence intervals around the actual survival curves.

Conclusion: Our new GoM model, applied to an external population, generated accurate predictions of survival using only the data from the patient's first visit. Any variable in the model can also be predicted, including specific cognitive and functional outcomes. The GoM model has great potential for the design and interpretation of clinical trials in three ways: 1) randomization can be optimized or evaluated by comparing the distribution of GoM status in control and treatment groups; 2) the model should predict disease progression well in the placebo group; individual deviations from model prediction in the treatment group could indicate specific treatment effects; 3) with sufficient validation, the model itself could be used in the place of a placebo group.

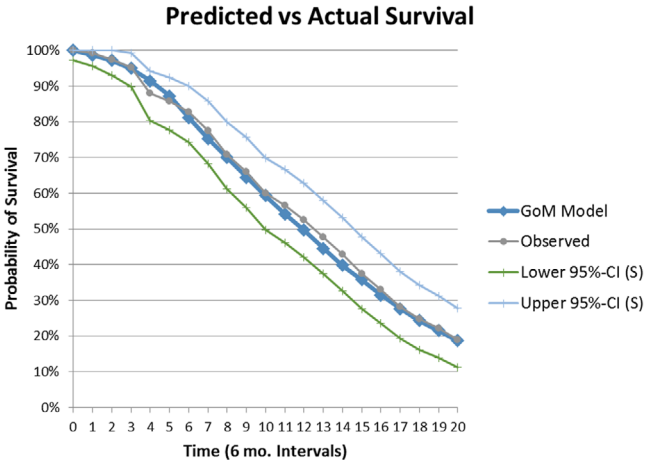
Predicted vs Actual Survival
Probability of Survival
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Time (6 mo. Intervals)
GoM Model
Observed
Lower 95%-CI (S)
Upper 95%-CI (S)

FIGURE 1