Global Brain Health Institute

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Prognostic Digital Biomarkers for MCI due to AD

Atlantic Fellows FOR EQUITY IN BRAIN HEALTH

Biomarker Risk Assignment Algorithm for Prognosis of Risk of Developing Mild Cognitive Impairment due to Alzheimer's Disease (MCI due to AD) in Cognitively Normal Subjects

Background

Altoida Inc is part of the 2018 EIT Health proposal Alzheimer's Disease Prediction Service (ADPS): digital biomarker for Real-World Evidence (RWE) in AD and following up the NCT02843529 study with the following purpose:

- To qualify the biomarker risk assignment algorithm composed of 4 domains (i.e. CSF, MRI, Cognition, APOE status), and age for prognosis of the risk of developing MCI due to AD within 5 years in cognitively normal individuals.
- To qualify the cognitive assignment algorithm composed of Altoida's Neuro Motor Index (A-NMI) and age for prognosis of the risk of developing MCI due to AD within 5 years in cognitively normal individuals.
- To compare the biomarker risk assignment algorithm (i.e. CSF, MRI, Cognition, APOE status) with A-NMI for age of onset for MCI due to AD in non-Caucasians and Hispanic/Latino Caucasians.
- End result of the study would be the development of a prognistic digital bookmarked for MCI due to AD risk assessment.

Epigenetic factors related to the variable biological liability to neurodegeneration that can be different among subjects with the same genotype, as well as education-related "cognitive reservoir" could moderate (either enhance or reduce) the primary effects of the ApoE/TOMM40 genotype. This variance could be reduced by including information on other biomarkers (e.g., beta-amyloid or tau-related signals) or on the performance to specific cognitive tests, in particular based on digital technology. The most advanced in its capacity to classify subjects at risk for developing MCI within 5 years is the Altoida Neuro Motor Index (A-NMI). This test, based on a smartphone app, has been used is several thousand individuals and is powered by an Artificial Neural Network classifier. It recently obtained the clearing of FDA in assisting diagnosis for AD since it could predict the occurrence of MCI within 5 years with a sensitivity of 94%.

Methods

A dataset of 685 individuals older than 73 year with ApoE genotyping were identified with abnormal preclinical Ab 42/40 ratio at the CSF. We measured 4 domains (i.e. CSF, MRI, Cognition, APOE status).

The Akaike Information Criterion (AIC) was used to compare models to one another to determine the model fit for a given set of biomarker variables and covariates. The AIC was selected for this purpose because it provides an index of the relative balance of model fit (based on the partial likelihood function for the Cox proportional hazards model) and model parsimony (based on the number of parameters in the model). A smaller AIC value indicates a better balance between fit and parsimony (Akaike, 1974).

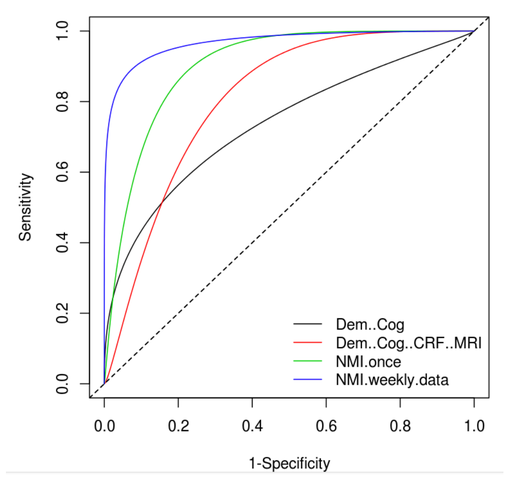
A combination of measures from the proportional hazards model was used, so that the area under the ROC curve (AUC) was maximised (Blanche et al., 2013). The optimal sensitivity and specificity cut-off point for each model was established using the Youden index (sensitivity + specificity 1) (Youden, 1950). The combined set of markers (from the 4 domains) with the higher AUC was considered to be more predictive of disease progression. AUC is widely considered a highly informative reflection of a measure(s) overall accuracy for predicting a disease-related outcome.

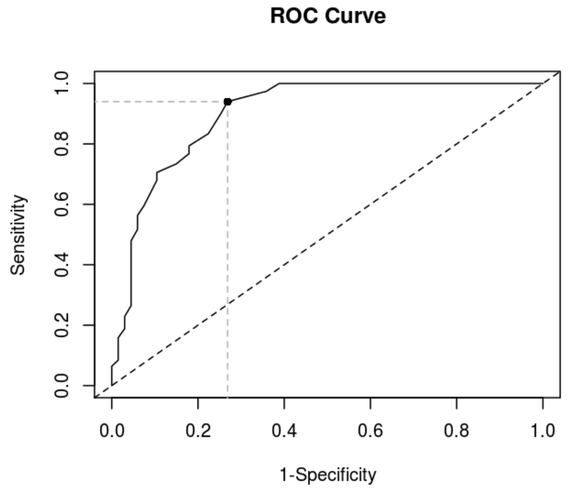
Lastly, different models were compared, using point-wise confidence intervals of the AUCs, against A-NMI done only once and A-NMI continuous data collection for 1 week at baseline for their ability to discriminate between participants who developed clinical symptoms and participants who remained normal.

In our case, the disease-related outcome was conversions from a cognitively unimpaired state to MCI due to AD diagnosis within 5 years. The study duration was the time needed to accumulate a total of 88 conversions to an adjudicated MCI due to AD diagnosis (the primary endpoint event) OR the time needed for all subjects who have not reached the primary endpoint event to complete a Year 6 Month 12 Visit without having converted to MCI.

Results

A nonlinear regression (Machine Learning) model was used to compute the functional impairment score. The ROC analyses presented here follow the example variables from the four primary domains evaluated in the BIOCARD study (Johns Hopkins University). These domains included: (i) CSF values; (ii) MRI measures; (iii) cognitive test scores; and (iv) APOE genetic status. We based the selection of which specific models should be included in the ROC analyses on findings from prior publications (Albert et al, 2018).





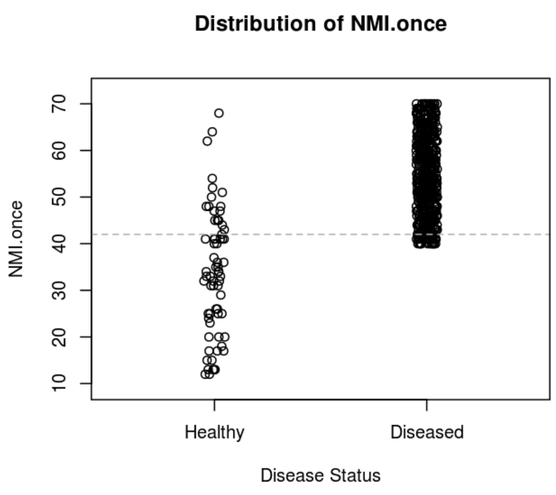


Table 1. Cut-off Results

Optimal cut-off method	Youden
Optimal cut-off point	78
Optimal criterion	0.7817725

Table 2. Performance Measures

	Value	Lower Limit	Upper Limit
Sensitivity :	0.812	0.775	0.845
Specificity :	0.970	0.896	0.996
Positive Predictive Value :	0.995	0.982	0.996
Negative Predictive Value :	0.409	0.355	0.854
Positive Likelihood Ratio :	27.189	6.939	106.542
Negative Likelihood Ratio :	0.194	0.161	0.234

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