Validation of a novel technology for non-invasive prognosis of amnestic MCI in clinics and clinical trials

Clinical Trials - Methodology

K. Vejdani*†, E. Khosravi*, T. Liebmann*, P. Krishnamurthy, and P. Kamali-Zare

* These authors have contributed equally to this study (co-first authors)

† Corresponding author (K. Vejdani): kvejdani@darmiyan.com

Darmiyan, Inc - San Francisco (United States)

ABSTRACT

Background

Objective, accurate, and reliable prediction of progression from mild cognitive impairment (MCI) to Alzheimer's dementia (AD) is a critical need in the evaluation and management of cognitive impairments, both in the clinical setting and for clinical trials. Neurocognitive assessments such as MMSE, MOCA, and CDR are routinely used for diagnosis at the time of clinical evaluation, but are relatively poor predictors of prognosis. For 5-year prognosis, the positive predictive value (PPV) is ~35% if the neurocog-based baseline diagnosis is MCI, ~50% if the diagnosis is amnestic MCI (aMCI), and ~ 70% if aMCI is also amyloid positive. As a result, nearly 30-50% of the selected amyloid-positive aMCI patients will not convert to dementia during the clinical trial period, making it extremely difficult to detect a statistically significant drug effect, if any.

Darmiyan Inc. has developed a novel technology, *BrainSee*, for objective, accurate, and reliable prediction of progression from aMCI to AD based on basic cognitive screening and standard, clinical brain MRI. The novelty of *BrainSee* lies in 1) subvoxel analysis of brain tissue to quantify deviation of microstructural parameters from their physiologic range, and 2) use of machine learning and AI to find disease-specific patterns of abnormality in the whole brain.

Objectives

The main objectives of this study were to evaluate:

1. The performance accuracy of *BrainSee* for 5-year prognosis of aMCI on blind samples coming from the real-world clinical setting
2. The robustness of *BrainSee* to standard routine clinical-grade data
3. Test-retest reliability of *BrainSee*
4. The clinical utility and usability of the output report of *BrainSee*, including the quantitative whole brain maps.

Methods

Data for third party validation were provided by the Knight ADRC (Washington University) Huntington medical research institutes (HMRI), Centre for aging and brain health innovation (CABHI), Baycrest Institute, University Health Network (UHN), and GERAS Hamilton Health Sciences (HHS). Subjects with amnestic MCI and without clinical depression or other significant medical, neurologic, or psychiatric disorders were selected for blind testing and validation of *BrainSee*, including performance accuracy and test-retest reliability. Patients with active use of substances, alcohol or anticholinergics were excluded. De-identified data including basic patient demographics (age, sex, education), MMSE, CDRSB, and MRI (T1, T2, DWI or DTI) were provided for analysis. *BrainSee*'s algorithm was blind to the distribution and clinical outcomes of all patients.

BrainSee processed each data point and generated a prognostic prediction of conversion to dementia within 5 years on a 4-point DarmiGrade scale, where grades 1 and 2 predict non-conversion and grades 3 and 4 predict conversion. Darmiyan's prognostic prediction was evaluated against the ground truth of a clinician's judgement of clinical outcome, i.e. the presence or absence of dementia at 5-year clinical follow-up. Progression to dementia at any point within 5 years was considered conversion. For non-conversion, absence of dementia for at least 5 years was required.

To account for class size imbalance, balanced accuracy (BA) was calculated as the arithmetic mean of sensitivity and specificity, i.e BA = (sensitivity + specificity) / 2. To account for class prevalence discordance between the sample and population, prevalence-corrected positive and negative predictive values (PPV_pc, NPV_pc) were calculated based on an assumed prevalence of 50% (based on known aMCI to AD conversion rate of 10-15% per year). To eliminate the bias effect of multiple time points for a single subject, a subject weighting strategy was used. For test-retest reliability, coefficient of variation was calculated for each subject and averaged over all subjects. In each subject, repeated clinical-grade or research-grade brain MRI scans were performed on the same day.

Results

For prognosis prediction testing, a total of 101 independent clinical time points (76 converter, 25 non-converter) from 95 subjects (74 converter, 21 non-converter) were provided by 3rd party investigators to Darmiyan for prognostic analysis. Subject ages ranged from 51 to 95 years, and male to female ratio was 1.175. For test-retest variability evaluation, sixty (60) subjects (78 scan sessions) were provided. The performance analysis results were reported as follows:

Balanced accuracy (BA) of prognostic prediction = 91.0 %
Sensitivity = 89.2 %, Specificity = 92.9 %
PPV_pc = 92.6 %, NPV_pc = 89.6 %
Test-retest coefficient of variation = 4.6%

These performance analysis results confirm the robustness of *BrainSee* to the variability in quality and resolution of research-grade and clinical-grade neuroimaging data.

Clinicians also indicated that *BrainSee's* report and grading system were easy to understand and interpret. *BrainSee*'s whole-brain maps were consistent with the predicted prognostic grades. These maps demonstrated quantitative regional differences between converter and non-converter aMCI patients.

Conclusions

Darmiyan's technology had a 91.0 % performance accuracy on blind clinical-grade brain imaging data from aMCI patients, and showed high test-retest reliability confirmed by third party investigators. Darmiyan's *BrainSee* technology is therefore an accurate, non-invasive and reliable tool to be used for prognostication of cognitive impairments in clinics and clinical trials.