P15

Clinical trials & Methodology

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

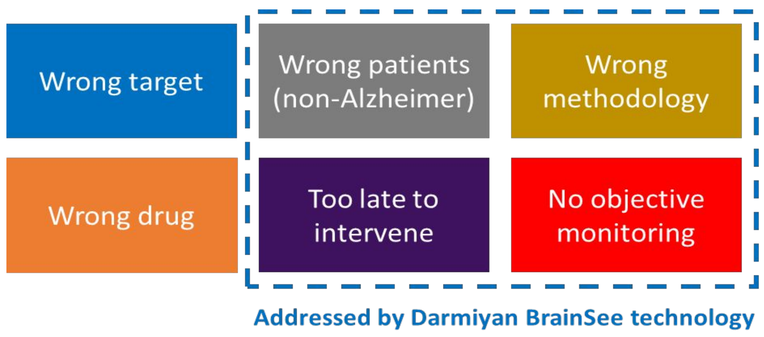
Kaveh Vejdani, Elham Khosravi, Thomas Liebmann, Pavan Krishnamurthy, & Padideh Kamali-Zare

Darmiyan, Inc., San Francisco, CA, USA

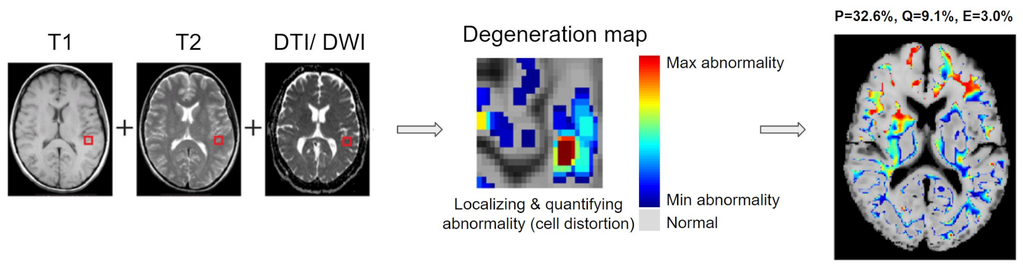
kvejdani@darmiyan.com

Background

- Darmiyan's novel *BrainSee* technology addresses four of the major reasons of Alzheimer's disease clinical trial failures, highlighted below:



- *BrainSee* is an AI-powered **virtual microscope** of the human brain that provides objective, accurate, and reliable prediction of progression from aMCI to AD. The input requirements are basic cognitive screening and standard clinical brain MRI. The novelty of *BrainSee* lies in 1) sub-voxel 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.



- **P or PND: P**ercent **N**euro-**D**egeneration, calculated as the number of abnormal voxels divided by the total number of voxels in a given brain region or slice
- **Q or QND: Q**uantitative **N**euro-**D**egeneration: Average percent deviation of the abnormal voxels from normal physiologic range, calculated as mean abnormality
- **E or END: E**stimated **N**euro-**D**egeneration, calculated as 100 x PND x QND

Objectives

To evaluate:

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

Methods

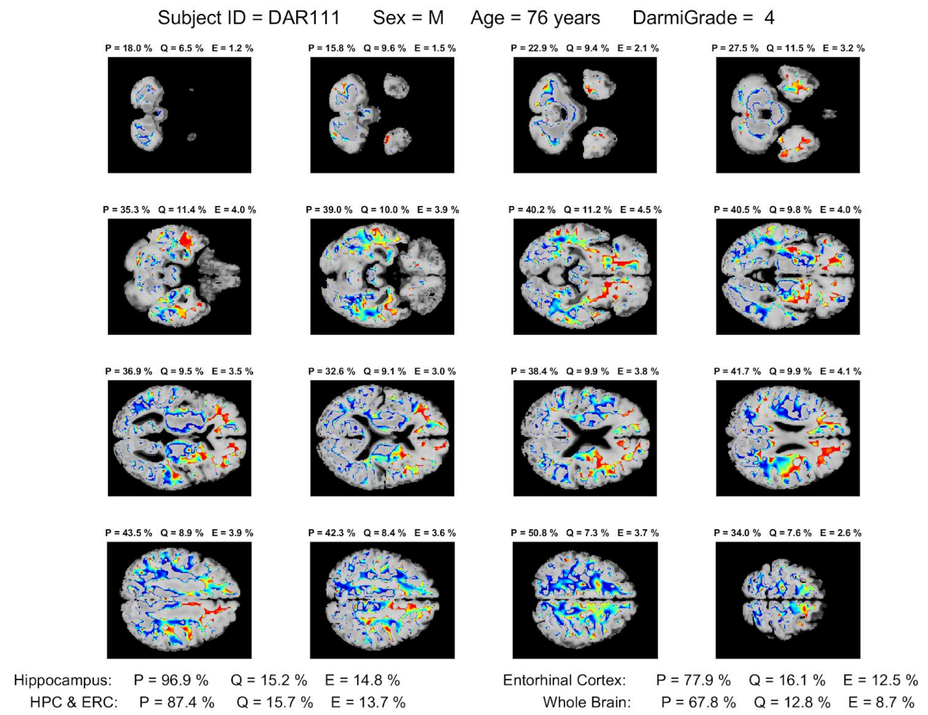
3rd party investigators: Stanford University, Huntington Medical Research Institutes (HMRI), Washington University in St. Louis, University Health Network (UHN), and GERAS Hamilton Health Sciences (HHS). The Canadian trial sites were coordinated by CABHI (Centre for Aging & Brain Health Innovation) following a CABHI-I2P2 (Industry Innovation Partnership Program) grant that was awarded to Darmiyan in 2018.

Data: Was provided by Knight ADRC (Washington University), Huntington medical research institutes (HMRI), Baycrest Institute, University Health Network (UHN), and GERAS Hamilton Health Sciences (HHS). De-identified data including basic patient demographics (age, sex, education), MMSE, CDRSB, and MRI (T1, T2, DWI or DTI) were provided for analysis. *BrainSee* was blind to the distribution and clinical outcomes of all patients.

Subjects: Amnestic MCI (aMCI), without clinical depression or other significant medical, neurologic, or psychiatric disorders. No active use of substances, alcohol or anticholinergics.

Processing: *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.

***BrainSee* report sample:**



Analysis & evaluation: 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 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

Total n = 101 time points (tmp) 95 subjects (sub)		*BrainSee* Predicted	
		Pos	Neg
Actual	Pos (n = 76 tmp, 74 sub)	66	8
	Neg (n = 25 tmp, 21 sub)	1.5	19.5

BA	Sen	Spec	PPV_pc	NPV_pc
91.0%	89.2%	92.9%	92.6%	89.6%

Note: 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).

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.

Impact on the Pharmaceutical industry:

This advanced novel technology can be used by pharma for:

1. Correct patient selection for AD trials

2. More sensitive and more frequent monitoring of drug effect

3. Companion diagnostic to enable global sales of AD drugs

4. Extract new insights from existing dementia databases