# Cognitive Endpoints for Early Alzheimer's Disease Trials: Development of the Early AD/ MCI Alzheimer's Cognitive Composite (EMACC)

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## THE METHODOLOGICAL QUESTION BEING ADDRESSED

What is the optimal method for endpoint selection for testing disease modifying drugs in Early Alzheimer's Disease (EAD)?

## BACKGROUND

As an alternative to current measures of clinical disease progression, a composite battery of objective neuropsychological tests that are distributed normally and sensitive to improvement OR decline may be more sensitive to a drug effect than clinical rating scales that were developed to track decline.

Data driven methods for establishing cognitive composite endpoints have been applied previously in preclinical AD (Donohue et al[1], Langbaum et al[2], Hassenstab et al [3]). Floor effects on these endpoints in EAD suggest a different cognitive composite may be required for later disease stages, so a cognitive composite suitable for global clinical trials in the Early AD or MCI stages of disease is needed.

## METHODS

We conducted parallel independent but identical analyses in 4 longitudinal cohorts of elders in which a total of 1,167 clinically normal (CN) β-amyloid negative (Aβ-; confirmed with amyloid PET imaging) and 516 individuals with confirmed Aβ+ PET scans meeting criteria for MCI or EAD (i.e. including also mild AD with CDR=0.5 or 1) were compared with respect to slope decline on a battery of neuropsychological tests. Cohorts included ADNI, AIBL, WUSTL and MCSA.(Table 1)* Neuropsychological test variables were restricted to those that could be reliably used in a global trial (i.e., not requiring a neuropsychologist to administer them, readily subject to linguistic/ cultural adaptation). Standardized slopes were computed within the EAD/MCI Aβ+ subgroup on all possible combinations of composites containing between 4 and 8 test variables and rank ordered. This step was conducted at years 2, 3 and 4. The EAD/MCI Alzheimer's Cognitive Composite (EMACC) was constructed from tests falling in the top ranked composites in each cohort at all time points. Effect size separation on EMACC from CN Aβ- controls at each time point was then compared to conventional endpoints (i.e. CDR Sum of Boxes (SB), Mini Mental Status Examination (MMSE)) using Linear Mixed Model (LMM) analysis.

Table 1.

| | ADNI | | AIBL | | WUSTL | | MCSA | |
|---|---|---|---|---|---|---|---|---|
| | CN Aβ- | MCI Aβ+ | CN Aβ- | MCI Aβ+ | CN Aβ- | MCI Aβ+ | CN Aβ- | MCI Aβ+ |
| N (baseline) | 186 | 237 | 278 | 121 | 155 | 57 | 548 | 101 |
| N Year 2 | 163 | 192 | 278 | 121 | 155 | 44 | 432 | 62 |
| N Year 3 | 84 | 156 | 233 | 69 | 135 | 33 | 337 | 47 |
| N Year 4 | 117 | 111 | 178 | 36 | 114 | 24 | 214 | 28 |

- Australian Imaging, Biomarkers and lifestyle (AIBL) study,
- Alzheimer's Disease Neuroimaging Initiative (ADNI)
- Knight Alzheimer's Disease Research Centre @Washington University St Louis (WUSTL).
- Mayo Clinic Study of Aging (MCSA)

## RESULTS

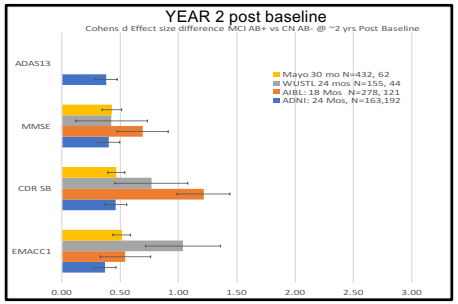
Commonalities of tests and domains measured were observed across the highest ranking (top 10) slope composites across time and across the 4 cohorts (i.e. word list learning was represented in almost all solutions and overall substantial overlap in test paradigms and cognitive functions measured was observed). The EMACC (see table 2) consists of validated measures of episodic memory, executive functioning, and processing speed. Overall the EMACC performed better or comparably to other endpoints and offers a cognitive endpoint for EAD trials. The AIBLE CDR effect size is likely larger than other cohorts at least in part because CDR raters also performed the neuropsychological tests and these results were known at the time of CDR rating. Additional details of the methods employed, sample characteristics, and preliminary validation of the EMACC are presented. (See figures).

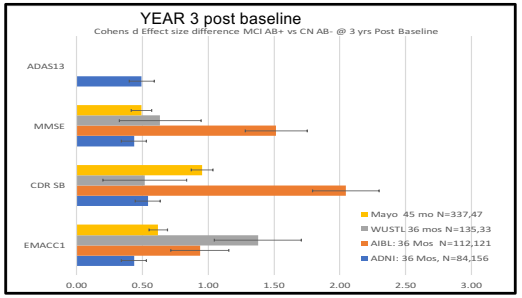
## Final Early /Mild AD Cognitive Composite (EMACC)

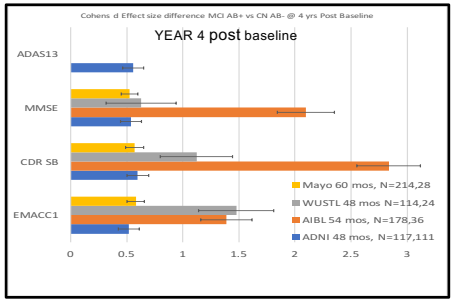
Table 2.

| | | ADNI | | AIBL | | WUSTL | | MCSA | |
|---|---|---|---|---|---|---|---|---|---|
| Domain | Paradigm | Test | Measure | Test | Measure | Test | Measure | Test | Measure |
| Memory | Word List Learning | RAVLT | Trials 1-5 | CVLT-II | Trials 1-5 | FCSRT | Free Recall | RAVLT | Trials 1-5 |
| | Digit Span | | | WAIS-R DS | Forward + Back | | Forward | | |
| Executive + Psycho-motor | Fluency | Category Fluency | Animals | Category Fluency | Animals + Boys Names | Category Fluency | Animals + Veg | Category Fluency | Animals + Fruits + Veg |
| | | | | Letter Fluency | FAS | Letter Fluency | FAS | | |
| | Trail Making | Trail Making Test | Trails A (secs) | | | Trail Making Test | Trails A (secs) | Trail Making Test | Trails A (secs) |
| | Conflict Inhibition | | Trails B (secs) | Stroop | Color Naming (secs) | | Trails B (secs) | | Trails B (secs) |
| | Coding | ADAS Number Canc. | Total Score | DSST | Total Score | DSST | Total Score | DSST | Total Score |

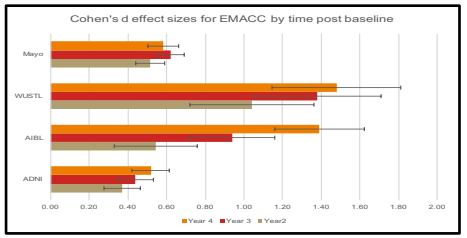
## Comparing Change on EMACC to other benchmarks




Effect size on EMACC by number of years post baseline




## CONCLUSIONS

The EMACC is a new and sensitive composite of well-known and validated neuropsychological tests that is suitable for examining the effect of disease modifying compounds on cognitive decline in the EAD or MCI stage of Alzheimer's disease.

**CITATIONS**

1. Donohue MC, Sperling RA, Salmon DP, et al. The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. *JAMA Neurol.* 2014;71(8):961-970.
2. Langbaum JB, Hendrix SB, Ayutyanont N, et al. An empirically derived composite cognitive test score with improved power to track and evaluate treatments for preclinical Alzheimer's disease. *Alzheimers Dement.* 2014;10(6):666-674.
3. Hassenstab J, Hagen CE, Han B, et al. Reliability and reproducibility of Cognitive Composites for Alzheimer's Disease Secondary Prevention Trials: The Power-PACC. 13th International Conference on Alzheimer's and Parkinson's Diseases; March 31, 2017, 2017; Vienna Austria.

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