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Establishing Composite Cognitive Endpoints for Use in Preclinical Alzheimer's Disease Trials

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Traditional cognitive outcomes developed for clinical trials in mild cognitive impairment (MCI) or Alzheimer's disease (AD) dementia are not well-suited for preclinical AD trials due to the psychometric properties of the tests (e.g., ceiling effects). Rather than selecting a single cognitive assessment that has been reported to measure change in preclinical AD, or individually examining multiple cognitive assessments and treating each as an individual outcome thereby potentially inflating Type I error, we and other groups have proposed using a composite cognitive test score as a primary endpoint in these preclinical AD trials (1–3). Composite endpoints have several advantages, including the ability to empirically derive the test score, and have it serve as single measure of multiple cognitive domains thus reducing the risk of Type 1 error.

As part of the Alzheimer's Prevention Initiative (API) we have proposed a strategy to empirically determine the combination of cognitive assessments that are most sensitive to detecting and tracking preclinical decline while controlling for practice effects and decline due to normal aging. This approach allows for the development of a composite cognitive test score of multiple cognitive domains with optimal sensitivity to preclinical AD cognitive decline. In addition, we have leveraged multiple, impendent, longitudinal datasets to help confirm a composite's sensitivity to detecting and tracking preclinical cognitive decline. The results from these efforts have help to inform the design of two API trials – the API Autosomal Dominant AD (ADAD) trial currently taking place in Colombia in partnership with Genentech and the University of Antioquia, and the API APOE4 trial currently in the planning stages in partnership with Novartis (4).

Under the auspices of the API, two independent, parallel efforts have been undertaken to identify composite cognitive test scores that are sensitive to detecting and tracking preclinical cognitive decline in (a) cognitively unimpaired ADAD mutation carriers (2), and (b) cognitively unimpaired older adults who subsequently progress to the MCI or AD

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dementia (1). Cognitive assessment data from the E280A Antioquia cohort (5) study and the Rush Alzheimer's Disease Center's cohorts (Religious Orders Study [ROS], Memory and Aging Project [MAP], and the Minority Aging Research Study [MARS]) (6–8) were used to derive the composites for these two populations at risk for ADAD and late-onset AD (LOAD), respectively. To derive the ADAD composite, analyses focused on cognitive assessment data from cognitively unimpaired PSEN1 E280A mutation carriers age 30 and older with at least two- or five-years of observational follow-up data. Data from the kindred non-carriers were used to control for effects due to practice and aging. To derive the LOAD composite, analyses focused on cognitive assessment data from initially cognitively unimpaired older adults who progressed to MCI or dementia during a two- or five-year follow-up period, using data from cohort participants who remained cognitively unimpaired during that same time period to control for effects due to practice and aging. In all analyses, every combination of cognitive assessments was examined and the mean to standard deviation ratio (MSDR) was selected as a measurement of sensitivity to the longitudinal decline for the combination of cognitive assessments, representing the coefficient of change (the mean of standardized change divided by the standard deviation of standardized change) (9). Due to the complexity of constructing a multivariate composite based on univariate or bivariate summary statistics, an integrated approach was used to evaluate all possible combinations of items to optimize the sensitivity resulting in an analysis that is mathematically closely related to principal component analysis (9). Results from these analyses were used as one way to assess the combinations and determine the optimal composite for each of the at-risk populations. Items that were consistently represented in the combinations with the highest sensitivity and that also demonstrated consistency within separate years of the two to five year time period were identified as robust items for measuring change. Construct validity was assessed by giving preference to combinations that represented cognitive domains known to decline due to AD that also had consistent sensitivity across the two and five years of decline.

Memory of Three Phrases was the most sensitive individual cognitive assessment to detect and track decline in E280A mutation carriers, with an adjusted five-year MSDR of 1.09. Logical Memory IIa - Delayed was the most sensitive individual cognitive assessment to detect and track decline in older adults who progressed to the clinical stages of LOAD in a two- to five-year time period, with an adjusted MSDR of 0.64.

Results from the optimized MSDR calculation for every possible combination of neuropsychological assessments indicate that the composite cognitive test score most sensitive to detecting preclinical cognitive decline in E280A mutation carriers, which has a five-year MSDR of 1.62, consists of: CERAD Word List – Delayed Recall, CERAD Constructional Praxis, CERAD Boston Naming (high frequency items), Raven's Progressive Matrices (Set A), and MMSE Orientation to Time (2). The optimized API LOAD composite, which has a five-year MSDR of 0.96, consists of: Logical Memory – Delayed Recall, East Boston Naming Test – Immediate Recall, Category Fluency (fruits and vegetables), Boston Naming Test (15 item), Raven's Progressive Matrices Subset (9 items), Symbol Digit Modalities, and MMSE Orientation to Time (1).

We and other groups have established that an empirically derived composite cognitive measure, that is also assessed for construct validity, is capable of detecting and tracking cognitive decline in individuals at particularly high risk for developing symptoms due to Alzheimer's disease (1–3). Notably, despite differences in the demographics characteristics and the neuropsychological assessment batteries in the cohort studies, the resulting composite cognitive test scores were quite similar in terms of the cognitive domains assessed. The two API composite cognitive test scores and the approach taken to develop them appears to fit into the framework provided by the Food and Drug Administration's recent draft guidance concerning a cognitive assessment serving as a primary efficacy measure in preclinical AD trials (10).

Additional efforts are underway under the auspices of the API to refine and extend these initial findings, helping to ensure their generalizability to other at-risk populations and demonstrate clinical relevance. For instance, we are refining the composites using a longer follow-up period and with a partial least squares (PLS) regression which optimizes both the combination of assessments and their weights at the same time, rather than relying on the implicit weighting of the test items. In addition, we are using other, independent longitudinal cohort study datasets to derive composite cognitive tests scores in order to extend the current findings and provide supportive evidence of the tests/cognitive domains included in the composite. The results from these efforts, which will be reported separately, will be important for the field as additional preclinical AD trials are implemented.

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