8-Year Disease Progression in Asymptomatic at Risk for Alzheimer Dementia (ARAD) Subjects from ADNI-1

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Objectives: The Preclinical Alzheimer Cognitive Composite (PACC) has been proposed as an end-point to measure cognitive decline in ARAD subjects. PACC decline was explored in 3 observational studies and exhibited amyloid related decline across cohorts except ADNI-1 where trajectories converged at 3-years. This analysis aimed to understand the characteristics of the decline of the PACC in ADNI-1.

Methods: Data were obtained from ADNI database on April 29th, 2015. The observed mean PACC decline was assessed in ARAD amyloid positive vs negative subjects. A portion (77/122: 63%) of these subjects volunteered to enroll in an extension phase beyond 3-years. PACC progression was assessed up to 8-years in extension subjects and additional analysis included comparison of extension and non-extension subjects; and analysis of sub-scale scores to understand the behavior of the composite.

Results: Amyloid negative subjects declined minimally in PACC over 8 years, while decline in amyloid positive subjects began after 3 years (Fig. 1). Over 3 years extension subjects declined less than non-extension subjects. Learning effects were seen for wordlist memory for 1 year and paragraph-recall for 3 years. The learning effect in paragraph-recall was probably related to multiple exposure of the same story. The executive function subscale exhibited high variability and relatively small longitudinal change. Finally, subjects correctly answered most test items on MMSE longitudinally and exhibited ceiling effects.

Conclusions: In ADNI-1, PACC exhibited ceiling and learning effects and may require longer follow-up in an intervention trial, however a PACC composed of alternative items may behave differently. The learning effect may be mitigated by using alternate equivalent forms of paragraph-recall, while the highly-variable subscales get down-weighted by their variability at baseline. This analysis is limited by small sample size and may represent atypically slower PACC progression since it is based on extension subjects who had less initial decline than non-extension subjects.
Figure 1. PACC Total Z-score in ADNI-1 Extension Subjects: PACC Change from Baseline as a Function of Baseline Amyloid Status. Grey shaded area represents the extension phase on the study.