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Commentary on Composite cognitive and functional measures for early stage Alzheimer's disease trials

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Demonstrating that disease-modifying treatments are effective and clinically meaningful across the Alzheimer disease (AD) continuum has led to the development of psychometric composites that attempt to capture a broad range of cognitive and functional changes characteristic of the AD trajectory. As Schneider and Goldberg (2019) point out, composite scales are not new to the clinical trial arena, but they are increasingly more attractive as treatment has moved into earlier preclinical stages of AD. Herein the authors provide a critical review of 12 such composites that were developed as primary outcome measures for AD clinical trials. They argue, however, that the development of these scales has been implemented without attention to basic psychometric principals, absence of alternate forms, and validation outside its use in the clinical trial (Schneider & Goldberg, 2019). They further argue that these composite measures may not fit the realities of the clinical phenotypes or neurobiology of AD.

In this commentary, we address several criticisms of the authors from our perspective of deriving composites for secondary AD prevention trials (specifically, the Preclinical Alzheimer's Cognitive Composite [PACC]). We will speak to (1) the value of cognitive composites in favor of a single cognitive test or domain score; (2) the psychometric validation of these composites prior to use in a clinical trial, and (3) considerations made in selecting PACC measures in the context of the clinical phenotype and neurobiology of AD.

Most clinical trials for AD have been completed at symptomatic stages of disease. Our field's recent shift toward secondary prevention has necessitated a corresponding evolution in cognitive outcomes that are able to capture more subtle cognitive change at the preclinical stage of AD. This need, combined with the available longitudinal and biomarker data from observational studies in older adults, has reenergized both neuropsychologists and statisticians to use both data-driven and theoretically driven approaches to develop and iterate on cognitive composites that can track decline along the AD trajectory, particularly for use in secondary prevention trials.

Part of the impetus for the creation of cognitive composites, is that the signal-to-noise ratio for cognitive decline is expected to be lower in preclinical AD, when many people are still cognitively normal. Composites by definition maximize signal-to-noise ratios. Although the AD phenotype is memory impairment, multiple large observational cohort studies show that cognition declines across executive functions, semantic memory, and global cognition in individuals with elevated amyloid β (Aβ).[1–3] Furthermore, recent work examining the heterogeneity of cognitive decline in early AD suggests that different atrophy patterns are associated with different cognitive trajectories.[4] Thus, domain-specific composites may underestimate or overestimate decline in a given participant in the context of phenotypic heterogeneity. Taken together, this suggests that a multi-domain cognitive composite is potentially more reflective of the multi-domain decline observed in preclinical AD and capable of capturing individual heterogeneity. A multi-domain composite that is sufficiently broad also has the inherent potential of being more clinically meaningful than performance on a single measure or domain. In line with this, we recently showed that subtle cognitive decline on the PACC over 3 years (> −0.14 to −0.26 standard deviation [SD] per year) was associated with a fivefold increased risk for diagnosis of MCI.[5]

The authors also raise concerns that many cognitive composites for early AD are not psychometrically validated, but this argument is not correct. In fact, most individual measures that constitute cognitive composites have extensive footprints in both the clinic and research and comprise well-validated tests with appropriate test-retest reliability and alternate forms. These standardized tests have been utilized in multiple longitudinal studies to track cognitive change both retrospectively and prospectively over 8 to 10 years in individuals with

AD biomarkers.[6–8] The PACC, as an example, is a composite, which includes the Mini Mental Status Exam,[9] the Free and Cued Selective Reminding Test,[10] the Digit Symbol Substitution Test,[11] and Logical Memory.[11,12] The tests used in the PACC were chosen, not only because of their theoretical emphasis on episodic memory but also from data-driven approaches that found additional changes in executive functions and global cognition in observational studies mirroring a secondary prevention population.[3] The ideal composite outcome for the A4 study would have to be one that was sensitive to Aβ-positive decline and could track neural networks involved in differentiating normal aging from the earliest stages of AD.[10] Finally, clinically normal individuals enrolled on the basis of positive biomarkers are likely to be at different stages of progression within the preclinical period,[13] thus, inclusion of measures such as the MMSE is relevant because small changes on this measure are clinically meaningful.

There are inevitable tradeoffs with different approaches. There are clinical trialists who are concerned that outcome measures are weighed down by items that add noise rather than contribute to capturing disease progression. They encourage the building of composites that lean in the direction of disease progression.[14] Some are adamant about randomizing test versions and/or test version order, whereas others advocate capitalizing on diminished practice effects.[15] In fact, repeated stimuli may be a reasonable approach in a disease characterized by diminished learning but deleterious if they interfere with capturing the efficacy of a treatment. Regardless, data from publicly available large cohort studies have afforded researchers the opportunity to develop cognitive composites using data-driven approaches based on a theoretical understanding of the AD trajectory. This has allowed for iterative improvement of composites using data, for example, movement from the PACC[3] to the PACC5,[16] which includes semantic memory that additionally tracts along temporolimbic networks and thereby increases the amyloid-related signal by 20% over 3 years. It is well-known that semantic memory is impaired in symptomatic AD, but the additional insight that semantic memory decline occurs much earlier, at the preclinical stage, suggests it would be appropriate for inclusion in the PACC.

A number of studies have now pooled data across multiple longitudinal observational cohorts. Despite the challenges of substituting different PACC measures based on cohort-specific tests (eg, using different memory measures across versions), the PACC exhibited relatively high concordance of baseline and slopes across the cohorts.[17,18] We think this is a testament to the robustness of the amyloid effect on cognition over time. Furthermore, it suggests that a cognitive composite that captures memory, executive functions, and global cognition is reliable in detecting change and that there may be flexibility in the individual measures used within that composite.[3]

We agree with Schneider and Goldberg (2019) that further exploration and optimization of cognitive end points for clinical trials are not only necessary but should be encouraged. However, we disagree that current cognitive composites were "uninformed by data, disregarded psychometric principals, overlooked the clinical phenotype and neurobiology of AD, and lacked independent validation" prior to use in a clinical trial. We are heartened by the multiple approaches to optimize and build better outcomes appearing in the literature and encourage continued thoughtful development. We need to work together to find an effective and meaningful disease-modifying treatment for AD. Establishing clinically meaningful cognitive outcomes is essential to that mission. Future generations are depending on it.

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