

# Establishing Clinical Relevance in Preclinical Alzheimer's Disease

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Converging evidence suggests that the pathophysiologic processes underlying Alzheimer's disease (AD) begin more than a decade prior to dementia (1, 2), starting with increased amyloid deposition followed by neurodegeneration and brain atrophy (3). Moreover, consensus is emerging that our best opportunity for intervention is likely prior to widespread neurodegeneration. For an anti-amyloid treatment to be effective, this may mean it will be necessary to treat the disease before symptoms appear. However, since by definition, the preclinical AD population does not have clinically detectable functional deficits, assessing the benefits of treatment becomes problematic.

Although cognition may be the earliest clinically relevant marker of disease progression, the temporal lag between the accumulation of AD pathology, cognitive decline and functional impairment remains to be elucidated. Evidence indicates that early cognitive decline is followed closely by subtle functional impairments in high-level everyday activities, suggesting that more sensitive measures of cognition and function may be useful as the best markers of early change.

## Assessing cognition and function in early stage disease

Connecting the dots between current cognitive and functional tests and clinically relevant markers of disease progression may be accomplished by a combination of: 1) updating traditional measures of function, 2) including more subjective measures of cognitive function, 3) developing performance-based functional measures, and 4) making cognitive tests more clinically relevant.

Several scales have been developed to assess activities of daily living (ADL) and instrumental ADLs (IADL) in clinical trials (4). In comparison to basic ADLs such as feeding, toileting, grooming, and bathing, IADLs represent more complex activities, such as managing finances and handling medications, which tap into cognitive abilities. Basic ADLs are typically impaired in moderate-to-severe AD, whereas decline in the ability to perform IADLs may occur at the MCI stage or earlier (5). A widely used IADL scale developed in 1997(6) has recently been updated by the Alzheimer's

Disease Cooperative Study (ADCS IADL) to include items relevant in the 21st century, such as using and remembering passwords, smartphones, and the Internet. Both study participants and partners may be assessed using IADL scales.

Subjective memory concerns have also been used to assess subtle cognitive decline in the earliest stages of the disease, and studies have demonstrated an association between amyloid burden and subjective cognitive complaints (SCC) among normal elderly (7, 8). A number of measures can be used to assess subjective cognitive concerns. For example, the ADCS Cognitive Function Instrument (CFI) includes both self-report and partner rating scales. The CFI is simple to administer, asking subjects and partners to compare current cognitive abilities to one year ago. For example, participants are asked "Compared to one year ago, do you have more difficulty managing money (e.g., paying bills, calculating change, completing tax forms)?" Participants may check either yes, no, or maybe; or in some instances "does not apply", and a score is calculated from these answers.

In a recent study, Amariglio et al (9) compared longitudinal scores on the CFI between "CDR progressors", i.e., subjects who progressed from CDR 0 to CDR 0.5 or 1.0, and "CDR stable", i.e., those who did not progress. CFI scores of CDR progressors separated early from the scores of CDR stable subjects and continued to increase over the four year time frame of the study, while scores of CDR stable subjects remained essentially unchanged. In the same study, the investigators showed that the CFI was able to differentiate subjects who were APOE $\epsilon$ 4 carriers from those who were not. Carriage of the ApoE $\epsilon$ 4 allele confers a substantially higher risk of developing sporadic, late-onset AD as well as an earlier age of onset (10). The study also examined the correlation between subjective CFI scores and objective cognitive testing, demonstrating that self and partner subjective ratings change at different rates. Initially, study partners' ratings are somewhat less correlated with the participants actual performance, but as the disease progresses and cognition worsens, CFI scores from the study partners' start to catch up. These changes may reflect the fact that individuals in the later stages of disease experience anosognosia, or lack of awareness of their impairments. The combination of self and partner

ratings therefore appears to correlate better with the cognitive testing than either alone.

### Is it clinically relevant?

Regulatory agencies require demonstration of the clinical relevance of outcome assessments. While some of the most widely used neuropsychological tests may indeed reflect neurological processes that are changing over the course of the disease, it remains a challenge to capture these early changes using clinically relevant tests. For example, connecting the dots on trail making tests may assess multiple cognitive processes such as attention, visual search, psychomotor speed, and planning (11), the relevance of this to an individual's everyday functional capacity has not been demonstrated. It may be that the best way to capture early cognitive decline with a clinically relevant scale is to employ performance-based functional assessments. Our group recently described a new performance based measure involving three high-level, real-life automated phone menu tasks frequently encountered by seniors: calling a pharmacy to refill a prescription, calling a health insurance company to select a new primary care provider, and making a bank transfer in order to have enough money to pay taxes (12). Performance on these tasks -- both time required to complete the task and number of errors -- was compared between clinically normal elderly and patients with MCI. For both of these measures, statistically significant differences were seen between the two groups. In addition, a subgroup of these subjects underwent magnetic resonance imaging (MRI), which showed that impaired performance was associated with inferior temporal cortical thinning in clinically normal subjects. This finding aligns with other studies suggesting that cortical thinning may be one of the earliest biomarker correlates of cognitive and functional decline (13, 14), and further supports the use of sensitive performance measures for the assessment of decline in the earliest stages of the disease.

In terms of making cognitive tests more relevant, tests of memory problems encountered in real life, such as remembering names and faces and pattern separation (ability to distinguish among very similar stimuli) may be especially sensitive in an aging population and particularly in the presence of amyloidosis (15). Moreover, for use as assessments to detect drug effects in clinical trials, repeated measures will be needed. Thus, computerized tests that provide frequent serial assessments may be especially useful. For use in the Dominantly Inherited Alzheimer's Network (DIAN) and Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) studies, we have developed an iPad version of a computerized cognitive composite -- CogState "plus" (16). This composite combines the CogState brief battery, which assesses reaction time, working memory, and incidental learning, along with face-name associative

memory and behavioral pattern separation tests.

We are getting closer to closing the gap between cognitive assessments and clinical relevance, but thorny issues remain with regard to current and planned secondary prevention trials. Longer trials will be needed to demonstrate clinically meaningful change, a consequence of which will be greater attrition. Moreover, functional change using current measures appears to be non-linear, speeding up as an individual approaches the MCI stage of the disease. What that means is that these measures will be challenging to use in delayed start designs.

The real-life relevance of early functional change also needs to be more clearly demonstrated. Insurance coverage is often linked to demonstrating financial benefit rather than improving quality of life, so it will be crucial to translate early functional impairments to financial consequences, for example demonstrating how errors on filling a prescription result in increased costs from inadequate treatment.

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