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Assessing cognition and function in Alzheimer's disease clinical trials: Do we have the right tools?

Peter J. Snyder[a], Kristin Kahle-Wrobleski[b], Stephen Brannan[c], David S. Miller[d], Rachel J. Schindler[e], Susan DeSanti[f], J. Michael Ryan[g], Glenn Morrison[h], Michael Grundman[i], Julie Chandler[j], Richard J. Caselli[k], Maria Isaac[l], Lisa Bain[m], Maria C. Carrillo[n,*]

[a]*Department of Neurology, Rhode Island Hospital & Alpert Medical School of Brown University, Providence, RI, USA*
[b]*Eli Lilly & Co, Inc., Indianapolis, IN, USA*
[c]*Takeda Development Center Americas, Inc., Deerfield IL, USA*
[d]*Bracket, Wayne, PA, USA*
[e]*Pfizer, Inc., New York, NY, USA*
[f]*Piramal Pharma Inc., Boston, MA, USA*
[g]*Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA*
[h]*Lumos Labs, San Francisco, CA, USA*
[i]*Global R&D Partners, LLC, San Diego, CA, USA*
[j]*Merck & Co., Whitehouse Station, NJ, USA*
[k]*Department of Neurology, Mayo Clinic Arizona, Scottsdale, AZ, USA*
[l]*European Medicines Agency (EMA), London, UK*
[m]*Independent Science Writer, Elverson, PA, USA*
[n]*Alzheimer's Association, Chicago, IL, USA*

Abstract Several lines of evidence from Alzheimer's disease (AD) research continue to support the notion that the biological changes associated with AD are occurring possibly several decades before an individual will experience the cognitive and functional changes associated with the disease. The National Institute on Aging—Alzheimer's Association revised criteria for AD provided a framework for this new thinking. As a result of this growing understanding, several research efforts have launched or will be launching large secondary prevention trials in AD. These and other efforts have clearly demonstrated a need for better measures of cognitive and functional change in people with the earliest changes associated with AD. Recent draft guidance from the US Food and Drug Administration further elevated the importance of cognitive and functional assessments in early stage clinical trials by proposing that even in the pre-symptomatic stages of the disease, approval will be contingent on demonstrating clinical meaningfulness. The Alzheimer's Association's Research Roundtable addressed these issues at its fall meeting October 28–29, 2013, in Washington, D.C. The focus of the discussion included the need for improved cognitive and functional outcome measures for clinical of participants with preclinical AD and those diagnosed with Mild Cognitive Impairment due to AD.

Keywords: Diagnostic criteria; Alzheimer's disease; Biomarkers

1. Introduction

Recent scientific advances in the understanding of the continuum of Alzheimer's disease (AD) pathology and related clinical symptoms have been accompanied by a burgeoning awareness of the considerable social and health system consequences of this disease if the current care

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*Corresponding author. Tel.: +1-312-335-5722; Fax: (866) 741-3716.
E-mail address: mcarrillo@alz.org

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paradigm is not significantly improved. Correspondingly, the US National Plan to Address AD, originally released in 2012 with planned annual updates [1], identified prevention and effective treatment of AD by 2025 as one of its primary goals. Achieving this ambitious goal has thus become a central focus of the Alzheimer's Association's Research Roundtable (AARR), a consortium of scientists from the pharmaceutical, biotechnology, imaging, and cognitive testing industries, which meets twice each year with regulatory, government and academic scientists to advance the development of new treatments for AD. On October 28 and 29, 2013, the AARR met to address what has become an urgent priority—the identification of appropriately sensitive tools to measure cognitive and functional change in the early stages of the disease. Several clinical trials are currently underway or in planning to study the early stages of AD, and harmonization of measurement efforts could streamline future trials and expedite drug approvals. Importantly, the focus of the AARR was to build consensus around key measurement properties rather than to settle on given scale (e.g., ADAS-Cog).

In February, 2013, the US Food and Drug Administration (FDA) issued a draft guidance on developing drugs for early stage disease [2], which addressed the need to use measures that demonstrate clinically meaningful cognitive and functional treatment effects. For those individuals nearing the onset of overt dementia, the draft guidance listed the Clinical Dementia Rating Sum of Boxes (CDR-SB) as an example of a suitable scale that assesses both cognitive and functional domains [3], but recognized that few assessment tools have been validated for use in persons at earlier stages of illness. At the same time, a perspective article authored by FDA scientists in the *New England Journal of Medicine* [4] acknowledged that it may not be feasible to assess functional impairment in the earliest stages of disease. The guidance suggested that in those cases, the accelerated approval mechanism [5] could be used to consider a single cognitive measure as the basis for market approval of a drug, contingent on post-approval studies to demonstrate a clinical benefit.

Further discussion was engendered by the coverage determination decision in September 2013 by the Centers for Medicare and Medicaid (CMS) regarding amyloid imaging positron-emission tomography (PET), in which they determined that under most circumstances, PET amyloid imaging would not be reimbursed except under Coverage with Evidence Development (CED) [6,7]. CED is a reimbursement mechanism that is being increasingly used to gather evidence in support of coverage for new technologies [8]. Relevant to the current discussion is the inclusion of clinical studies under the CED that have as a stated purpose to "develop better treatments or prevention strategies for AD, or, as a strategy to identify subpopulations at risk for developing AD." Appropriate instrumentation for these clinical studies is critical to help build the evidence base for use of PET amyloid technologies.

Both the FDA guidance and the CMS coverage determination provided more stimulation for the scientific community to converge on efforts that had already begun to address challenges for the assessment of early changes in cognition and function across the AD spectrum, and to demonstrate that those changes result in clinically meaningful outcomes.

2. The challenge of assessing cognition and function in early AD

The difficulty in assessing cognitive, much less functional, change in "presymptomatic" AD or very early mild cognitive impairment (MCI) stems in part from the fact that these individuals are relatively unimpaired and often without even mild subjective complaints. In addition, this population is extremely heterogeneous, with many confounding variables such as education and other lifestyle factors that may influence cognitive reserve [9] and the ability to detect early cognitive changes. Cultural, ethnic, and gender differences further complicate the assessment of cognition and function. Indeed, existing measures may assess somewhat different constructs across different cultural groups. Heterogeneity is further increased by the high intrinsic dimensionality of dementia, which arises from the nature of both baseline cognition and the dementing illness itself.

Neuropsychologists have identified a number of cognitive domains that are affected even in pre-symptomatic stages of AD. One of the first cognitive processes to show early functional change is episodic verbal memory [10]. The term "episodic memory" was coined by Endel Tuving in 1972 to distinguish remembering from knowing (semantic memory) [11]. Since that time, thousands of articles have been published about the nine discrete properties of episodic memory, which is now known to require prefrontal cortical and mesial temporal memory systems, the loci of early pathological changes in AD. Changes in episodic verbal memory assessed using list-learning tasks, such as the Rey Auditory Verbal Learning Test, are evident even before structural changes on MRI [12]. Cognitive markers such as logical memory, delayed, have also been shown to be more robust predictors of progression from MCI to AD than other biomarkers, including measurement of cortical thickness [13].

Longitudinal studies of generally younger apolipoprotein E ε4 (APOEε4) carriers, who are at increased risk for late onset and sporadic AD, have identified memory loss well ahead of executive skills or any other domain even in the setting of prefrontal amyloid deposition [14,15], while some studies of community dwelling older adults have identified executive skills as declining with or very soon after memory changes are evident, and within only a few years of MCI onset. Cumulatively, the evidence to date suggests that preclinical AD itself likely has an early stage characterized exclusively by subtle memory decline beginning over a decade before clinical onset, and a late stage within a few years of symptomatic MCI onset in