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Is cognitive decline measurable in preclinical Alzheimer's disease?

Sandra Weintraub[a], Christopher Randolph[b], Lisa Bain[c], James A. Hendrix[d,*], Maria C. Carrillo[d]

[a]*Cognitive Neurology and Alzheimer's Disease Center and Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA*
[b]*Department of Neurology, Loyola University Medical Center, Maywood, IL, USA*
[c]*Independent Science Writer, Philadelphia, PA, USA*
[d]*Division of Medical & Scientific Relations, Alzheimer's Association, Chicago, IL, USA*

As Alzheimer's disease (AD) drug development moves to earlier, preclinical stages of disease, clinicians, trialists, and regulators have wrestled with the question of how to detect cognitive change in people who, by definition, are cognitively normal. Addressing this challenge, the Alzheimer's Association's Research Roundtable (AARR) brought together in November 2016 an international group of experts involved in five ongoing prevention trials, along with other scientists from academia, industry, and regulatory agencies. Together, they discussed cognitive, functional, and biological measures that may serve as endpoints in secondary prevention trials targeting people in the prodromal stages of the disease.

The topic is of utmost importance for the aging society in our country and many other countries, said co-chair Sandra Weintraub, PhD, of Northwestern University. "The idea that we might be able to prevent the ravages of cognitive aging and Alzheimer's dementia holds a very exciting opportunity for us."

The first step, said Weintraub, is defining the target population for these prevention trials, which requires a deep dive into what constitutes normal cognition at different ages. Denise Park, PhD, director of research at the Center for Vital Longevity at University of Texas, Dallas, said this is a surprisingly difficult question, with no simple answer. With her colleagues, she has shown that test performance declines over the lifespan in "fluid" cognitive domains such as reasoning, working memory, and processing, but improves in "crystallized" domains such as vocabulary and world knowledge.

Once the neuropathological process of AD begins, and as much as 20 or 30 years before dementia becomes apparent, a variety of cognitive domains begin to decline in a continuous manner, according to research from population-based studies such as the Religious Orders Study (ROS) and Rush Memory and Aging Project (MAP), and cohort-based studies such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing (AIBL). Those studies have helped researchers identify cognitive domains to test in prodromal AD—including episodic memory, executive function, language, visuospatial perception, attention, and processing speed—and have led to the development of several cognitive batteries and composite measures that are being used in current prevention trials.

In addition, recent studies suggest that functional decline occurs even in cognitively normal individuals who later progress to mild cognitive impairment (MCI) or AD. These observations have led to the development of several functional measures that assess financial capacity, driving, computer usage, and everyday activities such as shopping. Performance-based measures as well as patient- and informant-reported outcomes have been developed and are being tested and validated across different populations to determine whether they provide additional clinically meaningful information about early disease progression that can guide drug development.

Biomarkers are also critical for drug development; however, so far none have been identified that are useful in tracking disease progression and response to treatment in early stages of AD. Some studies suggest that non-AD-specific markers of neuronal integrity, synaptic function, and inflammation may turn out to be useful, yet more research is needed in this area.

As with other Roundtable meetings, this one featured input from regulators, who emphasized the importance of

Weintraub and Randolph are co-first authors.
*Corresponding author. Tel.: +1-312-604-1650; Fax: +1-866-699-1246.
E-mail address: jhendrix@alz.org

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incorporating the patient voice into all aspects of trial design, including the selection of endpoints. Regulators have been true partners in developing the science around AD clinical trials, said Maria Carrillo, PhD, chief science officer at the Alzheimer's Association. "We are all in this together," she said.

Co-chair Christopher Randolph, PhD, of MedAvante and Loyola University Medical Center closed the meeting, noting, "We have a lot of harmony around how to measure early neurocognitive change and even how to measure non-cognitive clinical changes that occur in the preclinical phase." He added that there is still work to be done on nomenclature and defining a path to clinical meaningfulness.

A more detailed report of this meeting will appear in a future issue of *Alzheimer's & Dementia*.