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2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

The National Institute on Aging and the Alzheimer's Association Research Framework for Alzheimer's disease: Perspectives from the Research Roundtable

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Abstract The Alzheimer's Association's Research Roundtable met in November 2017 to explore the new National Institute on Aging and the Alzheimer's Association Research Framework for Alzheimer's disease. The meeting allowed experts in the field from academia, industry, and government to provide perspectives on the new National Institute on Aging and the Alzheimer's Association Research Framework. This review will summarize the "A, T, N System" (Amyloid, Tau, and Neurodegeneration) using biomarkers and how this may be applied to clinical research and drug

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development. In addition, challenges and barriers to the potential adoption of this new framework will be discussed. Finally, future directions for research will be proposed.

Keywords: Alzheimer's disease; Amyloid; Tau; Neurodegeneration; Clinical trials; Biomarkers

1. Introduction

The identification of Alzheimer's disease (AD) biomarkers and their ability to measure pathology antemortem has led to a fundamental reconsideration of the pathogenesis of AD. The importance of biomarkers was already reflected in revised diagnostic criteria proposed by the National Institute on Aging and the Alzheimer's Association in 2011 [1–4] and the International Working Group in 2007 [5]. The International Working Group criteria were subsequently updated in 2010 [6] and 2014 [7]. With each of these iterations, the field has achieved greater sensitivity and specificity of AD diagnoses, which in turn has better enabled our ability in clinical trials to test hypotheses of treatment and ultimately prevention of AD.

Beginning in 2016, the NIA and AA convened a new workgroup to develop a research framework for AD that embodied the paradigm shift occurring in the field. Rather than conceptualizing AD primarily as a clinicopathological entity, biomarkers have demonstrated that AD pathology exists over the continuum of the disease–from a stage preceding overt symptomatology (the "preclinical state") to the progressively more impaired symptomatic states of mild cognitive impairment (MCI) and dementia. The same biomarkers have also shown in greater resolution how dementia may occur in people with both AD and non-AD pathology.

The National Institute on Aging and the Alzheimer's Association Workgroup's Research Framework uses a biomarker classification scheme proposed by Jack et al [8], which divides the current major AD biomarkers into three categories, based on the type of pathologic change each measures: β-amyloid (A), pathological tau (T), and neurodegeneration (N). The framework is intended to provide the research field with a common language for diagnostic purposes. Its scope is therefore focused on those aspects of research involving humans where specificity of the diagnosis of AD is important. Although the framework contains certain assumptions about diagnostic relevance to AD, it should not be conceived as a mechanistic hypothesis about the pathogenesis of AD. An important goal of this effort is to speed up and improve the development of disease-modifying treatments for AD.

A draft of the framework was presented at the Alzheimer's Association International Conference in July 2017, and an updated draft was posted online in November 2017 [9], with the intent of collecting comments from the research community. Given the importance of this issue, the Alzheimer's Association's Research Roundtable convened scientists from academia, industry, and government in the of Fall 2017 to discuss the framework.

2. The ATN system

The ATN nomenclature represents a conceptual framework that is based on the past decade's empiric observations of relationships between markers of amyloid, tau, and neurodegeneration. "A" refers to amyloid β (Aβ) as measured either by amyloid positron emission tomography (PET) imaging of amyloid plaques or in the cerebrospinal fluid (CSF) as $A\beta_{42}$ or the $A\beta_{42}$ to $A\beta_{40}$ ratio. "T" refers to tau pathology as measured by CSF phosphorylated tau or tau PET imaging of parenchymal neurofibrillary tangles. "N" refers to neurodegeneration or neuronal injury and dysfunction, as measured for example by hippocampal volume or cortical volume or thickness. While "A" and "T" are considered to have diagnostic specificity for AD, "N" is not specific for AD diagnoses because it can reflect any number of etiologies in addition to AD. The roundtable discussion devoted several sessions to understand the details of each category of biomarkers, which is summarized below.

2.1. Classification and staging with ATN

The ATN biomarkers may reflect the presence (state) or progression (stage) of a disease. State biomarkers indicate the presence or absence of pathology and by extrapolation, the presence or absence of a disease. In AD, the $A\beta_{42}$ peptide, deposited in a β-pleated sheet conformation in cored or neuritic plaques, is the principal state biomarker defined neuropathologically [10]. Biomarkers of amyloid pathology are the first to change in dominantly inherited AD [11]. In persons without dominantly inherited mutations, elevations of PET amyloid can also appear in some cognitively normal 50- and 60-year-olds anticipating incident dementia by roughly 15 years [12]. The neuropathological definition [10] of AD drives the ATN definition of AD and requires the presence of amyloid plaques (as evidenced by PET or CSF) for diagnosis.

Elevated numbers of amyloid plaques have long been considered necessary but not sufficient for the diagnosis of AD neuropathologically. The debate over the centrality of elevated Aβ peptide in AD pathogenesis is a separate matter; to be sure, there is much controversy regarding Aβ peptide's role in causing AD. But diagnostically, this is a settled issue as far as a necessity for the majority of the field: a minimum burden of amyloid plaques (composed of the $A\beta_{42}$ peptide) is necessary for the diagnosis of AD. In 2012, the