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# ALZHEIMER'S DISEASE REDEFINED:
# NEW RESEARCH FRAMEWORK DEFINES ALZHEIMER'S
# BY BRAIN CHANGES, NOT SYMPTOMS

**Chicago, April 10, 2018 –** "NIA-AA Research Framework: Towards a Biological Definition of Alzheimer's Disease" was published today in the April 2018 issue of Alzheimer's & Dementia: The Journal of the Alzheimer's Association. First author Clifford R. Jack, Jr., M.D., of Mayo Clinic Rochester, MN and colleagues propose shifting the definition of Alzheimer's disease in living people – for use in research – from the current one, based on cognitive changes and behavioral symptoms with biomarker confirmation, to a strictly biological construct. This represents a major evolution in how we think about Alzheimer's.

Understanding and effectively treating Alzheimer's disease and other dementias may be the most difficult challenge for the medical/scientific community this century. The field has experienced monumental challenges developing new and effective drug therapies, not the least of which was the discovery that – until recently –clinical trials were conducted where up to 30% of participants did not have the Alzheimer's disease-related brain change targeted by the experimental drug.

"With the aging of the global population, and the ever-escalating cost of care for people with dementia, new methods are desperately needed to improve the process of therapy development and increase the likelihood of success," said Maria Carrillo, Ph.D., Alzheimer's Association chief science officer and a co-author of the new article. "This new Research Framework is an enormous step in the right direction for Alzheimer's research."

According to the authors, "This evolution of the previous diagnostic criteria is in line with most chronic diseases that are defined biologically, with clinical symptoms being a … consequence." They say, "the goal of much of medicine is to identify and treat diseases prior to overt symptoms. The [NIA-AA Research] Framework is intended to provide a path forward to … prevention trials of Alzheimer's disease among persons who are clinically asymptomatic."

Other areas of medicine have used this approach to define disease processes using biomarkers, for example: bone mineral density, hypertension, hyperlipidemia and diabetes are defined by biomarkers. Therapies that address these biomarkers have been shown to reduce the likelihood of developing fractures, heart attacks and strokes.

The authors, "take the position that biomarker evidence of Alzheimer's disease indicates the presence of the disease whether or not symptoms are present, just as an abnormal HbA1C indicates the presence of diabetes whether or not symptoms are present."

In 2011, the Alzheimer's Association (AA) and the National Institute on Aging (NIA) at the U.S. National Institutes of Health convened experts to update the diagnostic guidelines for Alzheimer's disease. The landmark publications designated three stages of Alzheimer's – preclinical (before symptoms affecting memory, thinking or behavior can be detected), mild cognitive impairment and dementia. In bringing together global leaders again in 2017 to review advances in the field and update the guidelines, a profound shift in thinking occurred to define Alzheimer's disease biologically, by pathologic brain changes or their biomarkers, and treat cognitive impairment as a symptom/sign of the disease, rather than its definition.

According to Dr. Jack, once validated in diverse global populations, this new definition will create a powerful tool to speed and improve the development of disease-modifying treatments for Alzheimer's disease.

The authors envision that defining Alzheimer's disease as a biological construct will enable a more accurate understanding of the sequence of events that lead to the cognitive impairment associated with Alzheimer's disease, as well as the multiple causes of the disease. This will enable a more precise approach to therapy trials including focusing more specific targets and including the appropriate people.

In an accompanying editorial, Ara S. Khachaturian, Ph.D., Executive Editor, and the editorial staff of Alzheimer's & Dementia, "commend the effort within the Research Framework to create a common language that may lead to new thinking for the generation of new testable hypotheses about the conceptual basis for Alzheimer's disease. Such a language is a critical and essential element in addressing the ongoing challenge of developing more intricate and comprehensive models of Alzheimer's disease … for the identification of new interventions and diagnostics."

In their "Editorial comment to the 'NIA-AA Research Framework: Towards a Biological Definition of Alzheimer's Disease,'" Nina Silverberg, Ph.D., Cerise Elliott, Ph.D., Laurie Ryan, Ph.D., Eliezer Masliah, M.D., and Richard Hodes, M.D., of NIA point out that the Framework – in addition to improving early detection and the development of new therapies – could potentially "allow more precise estimates of how many people are at risk [for or living with] Alzheimer's disease, how best to monitor response to therapies, and how to distinguish the effects of Alzheimer's disease from other similar pathologies."

Anticipating questions on the impact of the NIA-AA Research Framework on research funding, they add that, "The NIH will consider research applications using the Framework as well as proposals using alternative schemes when designing experimental approaches. The NIH continues to welcome applications where biomarkers may not be appropriate."

In the article, the authors say they, "appreciate the concern that this biomarker-based Research Framework has the potential to be misunderstood and misused. Therefore, we emphasize: First, it is premature and inappropriate to use this Research Framework in general medical practice. Second, this Research Framework should not be used to restrict alternative approaches to hypothesis testing that do not employ biomarkers … biomarker-based research should not be considered a template for all research into age-related cognitive impairment and dementia."

That said, the authors believe that Framework applies to the entire Alzheimer's disease research community. In the drafting of the document, "we were careful to include … representatives of the Industry and the Food and Drug Administration in addition to government and non-governmental organizations. Finally, the Framework was vetted with numerous stakeholders at several meetings as well as posted for months for public comment."

"It is called a 'Research Framework' because it needs to be thoroughly examined – and modified, if needed – before being adopted into general clinical practice," Dr. Jack said. "Importantly, this Framework should be examined in diverse populations."

The authors recognize that the current form of the NIA-AA Research Framework is designed around only the biomarker technology that is presently available. They point out that the proposed biomarker scheme (see the attached fact sheet) is expandable to incorporate new biomarkers, as they are developed and verified.

**About Alzheimer's & Dementia: The Journal of the Alzheimer's Association**
The mission of Alzheimer's & Dementia: The Journal of the Alzheimer's Association is to bridge knowledge gaps across a wide range of bench-to-bedside investigations. The journal creates a forum for rapid communication of new findings, ideas and perspectives; increases knowledge in diverse disciplines to promote early detection/diagnosis and/or interventions; and provides the scientific impetus for new initiatives or public policies concerning research on prevention and new models of health services. Visit www.alzheimersanddementia.com.

**About the Alzheimer's Association**
The Alzheimer's Association is the leading voluntary health organization in Alzheimer's care, support and research. Our mission is to eliminate Alzheimer's disease through the advancement of research; provide and enhance care and support for all affected; and reduce the risk of dementia through the promotion of brain health. Our vision is a world without Alzheimer's®. Visit http://www.alz.org or call 800.272.3900.

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NOTE: Media are directed to a news release by the National Institute on Aging at the U.S. National Institutes of Health on this topic.

Disclosures: Alzheimer's Association staff members Maria Carrillo, Ph.D., Chief Science Officer and Heather Snyder, Ph.D., Senior Director of Medical and Scientific Operations are co-authors on "NIA-AA Research Framework: Towards a Biological Definition of Alzheimer's Disease."

**"NIA-AA Research Framework: Towards a Biological Definition of Alzheimer's Disease"**

**Fact Sheet**

What It Is
*   In the NIA-AA Research Framework, Alzheimer's disease is defined by its underlying pathologic processes that can be documented by post-mortem examination or in vivo by biomarkers.

*   In a research setting, diagnosis is not based on the clinical consequences of the disease (i.e. symptoms/signs).

*   It shifts the definition of Alzheimer's disease in living people from a syndromal (a group of symptoms that consistently occur together) to a biological construct.

The AT(N) Biomarker System
*   AT(N) nomenclature represents a conceptual framework that is based on the past decade's observations of relationships between markers of amyloid, tau, and neurodegeneration.
    -   "A" refers to $A\beta$ as measured either by amyloid positron emission tomography (PET) imaging of amyloid plaques or in the cerebrospinal fluid (CSF) as $A\beta42$ or the $A\beta42$ to $A\beta40$ ratio.
    -   "T" refers to tau pathology as measured by CSF phosphorylated tau (p-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, cortical volume/thickness, or CSF total tau (T-tau).
*   While "A" and "T" are considered to have diagnostic specificity for Alzheimer's disease, "(N)" is not specific for Alzheimer's disease diagnoses.

*   The AT(N) system was designed with both a CSF and an imaging biomarker in each of the three biomarker groups.

*   Complete AT(N) biomarker characterization of research participants is possible using either imaging or CSF biomarkers alone. Some groups may prefer a mixture of imaging and CSF biomarkers.

*   The AT(N) system does not imply a specific order of events nor does it imply causality. It is a system for grouping biomarkers and classifying research participants on the basis of biomarker profiles.

Applications of AT(N) in Clinical Trials
*   Selecting participants for Alzheimer's disease dementia or MCI trials based on the AT(N) scheme would enrich the trial with persons with the greatest likelihood of decline in the time frame of a clinical trial.

- Perhaps the greater advantage afforded by the AT(N) Framework is that it could enable more precise staging of individuals along the Alzheimer's disease continuum. This would allow future proof-of-concept trials to be conducted in biologically-defined (in addition to clinically-defined) target populations, and to more directly investigate whether modulation of a specific target interferes with a specific component of disease pathologic change.

- Innovative clinical trial approaches that have proven successful in other disease areas such as oncology (e.g., platform trials, umbrella and basket designs) might be employed with stratification of subjects by AT(N) profile, enabling a data-driven approach to identify the biological stage of disease in which an intervention has maximal treatment effects.

- If successful, trials in biologically defined populations could address uncertainties that have thus far stymied Alzheimer's disease drug development: Is amyloid a trigger or driver of downstream neuropathology? What is the latest biological stage of Alzheimer's disease at which secretase inhibition slows progression? At what stage will tau-directed therapies be effective in slowing progression of tau pathology?

Why It's Better than What We Have Now
- [T]here are two enormous pitfalls with using symptoms to define Alzheimer's disease; they are neither sensitive nor specific for the neuropathologic changes that define the disease, and they cannot identify individuals who have biological evidence of the disease but do not (yet) manifest signs or symptoms.

- The most rational framework with which to discover interventions that prevent or delay the initial onset of symptoms is a biologically based definition of the disease that encompasses both the clinical and the preclinical phases.

- Thus a Framework suitable for interventional trials should be founded on a biologically based definition of Alzheimer's disease; and, it is only rational that the Framework is harmonized across interventional and observational research.

- The notion of providing a common language with which researchers can communicate consistently is important.

- Because clinical trials are a multinational effort in the 21st century, developing a common language for biomarker designations in the Alzheimer's disease spectrum is critical for harmonization across the international roster of clinical trial sites and investigators.

- If one research group defines Alzheimer's disease as β amyloid plaques and pathologic tau while a different group defines Alzheimer's disease as the presence of amnestic dementia then findings from the two groups point to different entities and conclusions are not directly comparable.

- Personalized medicine: The AT(N) system moves Alzheimer's disease research in the direction of personalized medicine by coding pathologic change in three categories for each research participant and allows for future flexibility by adding other biomarkers as they are discovered and validated.

- This level of granularity in biomarker classification, combined with genetic and clinical information, will presumably be useful in tailoring treatment to the individual when appropriate specific treatments become available.

<u>New Language and Labels</u>

- An individual with biomarker evidence of Aβ deposition alone with a normal pathologic tau biomarker would be assigned the label "Alzheimer's pathologic change."

- The term "Alzheimer's disease" would be applied if biomarker evidence of both Aβ and pathologic tau was present.

- Alzheimer's pathologic change and Alzheimer's disease are not regarded as separate entities but earlier and later phases of the "Alzheimer's continuum" – an umbrella term that includes both.

- These definitions are applied independently from clinical symptoms.

- Every research participant has both a biomarker profile and a cognitive stage. For example, in the Research Framework the label "Alzheimer's disease with MCI" is used rather than "MCI due to Alzheimer's disease (2011)."
    - By this we indicate that although the person has an Alzheimer's disease biomarker profile, we cannot know if the cognitive deficit is attributable to Alzheimer's disease alone or to other potential comorbidities in addition.

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