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Accurately Diagnosing Alzheimer's Disease: Shortcomings of Blood Biomarkers and Need for Definitive, Non-invasive Diagnostic Testing

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This paper is intended to support stakeholders in the healthcare ecosystem that are impacted by AD.

Part I.
A. Complexity and Prevalence of Alzheimer's Disease vs. Early Dementia or Mild Cognitive Impairment

B. Alzheimer's Association Cautions Use Recommendations for Blood Biomarkers in Diagnosing AD

Part I. Complexity and Prevalence of Alzheimer's Disease vs. Early Dementia or Mild Cognitive Impairment

Alzheimer's disease (AD) is the most common form of dementia and the sixth leading cause of death in the United States (US).[i] In the US, an estimated 6.2 million Americans are living with AD, for which there is neither a cure nor an FDA-approved tool to definitively diagnose AD in a living patient.[ii] As a result, the traditional approach for diagnosing AD is inadequate to identify appropriate candidates for the new treatments which are already stirring controversy in public and private sectors.

A challenge to correctly diagnosing AD is that many symptoms can be similar to other types of dementia.[iii] Individuals can be asymptomatic for years before showing cognitive decline, termed the preclinical stage.[iv] During this timeframe, there is a build-up of a protein called β-amyloid (Aβ) and tangled clumps of tau protein. However, mounting evidence suggests that a primary pathologic feature of AD is the loss of synapses: the multiple sites distributed throughout the brain at which neurons communicate with one another.[v] People in the clinical stage of disease begin to display mild cognitive impairment (MCI), which includes memory loss, and visual or spatial problems. Synaptic loss is correlated with the severity of cognitive decline in patients with AD.[vi]

Unfortunately, AD is progressive, such that cognitive and functional impairments become increasingly more severe, eventually resulting in the loss of independence and death.[vii] AD is the most common cause of dementia, accounting for 60-80% of dementia, a general term for cognitive and memory loss usually serious enough to interfere with a person's daily life.[viii]

Symptoms of MCI are not as severe as the symptoms of AD or dementia, although it may progress to dementia or AD over many years. For people diagnosed with MCI, within just one year 10%-15% of them will go on to develop dementia and one-third of those with MCI will develop AD (the most common form of dementia) within five years.[ix,x] People with MCI do not experience the personality changes or other problems that are characteristic of AD, are still able to take care of themselves and do their normal daily activities.

To date, the only definitive method to diagnose AD in clinically demented patients is through *post-mortem* evaluation of the brain to identify the accumulation of Aβ plaques and the aggregation of p-tau protein into abnormal accumulations that collect inside neurons (known as neurofibrillary tangles).[xi] This Gold Standard is based on the 1991 Consortium to Establish a Registry for Alzheimer's Disease (CERAD).[xii] More than half of AD patients also have other pathologies of dementia, further complicating the diagnostic process.[xiii]

Role of β-amyloid peptide (Aβ)

- The development of AD has been hypothesized to be driven by the production and deposition of the β-amyloid peptide (Aβ) and / or neurofibrillary tangles. Investigators have long been puzzled by the weak to nonexistent correlation between the amount of amyloid plaques -- also known as neuritic plaques, Aβ plaques or senile plaques – together with the intraneuronal neurofibrillary tangles -- and the degree of clinical dementia.[xiv]

Recent advances in understanding of the development of amyloid pathology have helped solve this enigma. Substantial evidence now indicates that the soluble forms of Aβ, and the quantity of Aβ in different pools, may be more closely related to the disease state. Aβ plaques and neurofibrillary tangles are hallmarks of disease at death.

Given the benefit, risk and cost burdens of new drugs now being introduced, clinicians and payers need better tools to identify AD in people recently diagnosed with dementia, even when the dementia is caused by several factors.

Blood biomarkers indicate biological changes in the body that can be reliably measured to indicate the presence or absence of a disease, or the likelihood of later developing a disease.[xv] While they have the potential to help clinicians screen for the presence of amyloid plaque or tau, hallmarks of AD, they do not diagnose MCI or early AD dementia with high accuracy. Additional studies are warranted as co-morbid conditions such as chronic kidney disease and other conditions that may affect the reference ranges for the blood biomarkers.[xvi] In fact, the Alzheimer's Association states further research is needed before widespread use of BBMs, as explained below.[xvii]

Alzheimer's Association Cautions Use Recommendations for Blood Biomarkers in Diagnosing AD

While blood-based markers (BBMs) have recently shown promise to revolutionize the diagnostic and prognostic work-up of AD, as well as to improve the design of interventional trials, the Alzheimer's Association states in detail that further research is needed before widespread use of BBMs can be recommended.[xviii]

The Association aims to provide appropriate use recommendations for use of these BBMs in clinical practice and trials. To this aim, they discuss the current need for biomarkers, briefly summarize the state-of-the-art results for the most promising BBMs and, more importantly, define research priorities needed to fill significant knowledge gaps. Finally, they describe the consensus appropriate use recommendations defined by this expert group for use of BBMs in the clinic as well in trials.

Authors assert that they already now recommend use of BBMs as (pre-) screeners to identify individuals likely to have AD pathological changes for inclusion in trials evaluating disease-modifying therapies, provided the AD status is confirmed with positron emission tomography (PET) or cerebrospinal fluid (CSF) testing. They also encourage studying longitudinal BBM changes in ongoing as well as future interventional trials.

However, they advise that BBMs should not yet be used as primary endpoints in pivotal trials and further recommend to cautiously start using BBMs in specialized memory clinics as part of the diagnostic work-up of patients with cognitive symptoms.[xix] The results should be further confirmed whenever possible with CSF or PET, expensive diagnostics that may not be available or affordable for certain communities. Additional data are needed before use of BBMs as stand-alone diagnostic AD markers or before considering use in primary care.

Currently there is no known cure for AD, but with strides in diagnostics and research and drug commercialization underway, valuable treatment of this fatal condition will become available. Clinical diagnosis of AD in living patients is an ongoing pursuit with a great focus on biomarker-based approaches.

In part 2 of this white paper, we will address pathways for diagnosis and treatment.

About Synaps Dx

SYNAPS Dx is a privately held company focused on the research, development and commercialization of a diagnostic test for Alzheimer's disease (AD). The Company offers DISCERN™, the first highly accurate, minimally invasive test supporting a clinician's definitive diagnosis of AD versus other forms of dementia, even in people recently diagnosed with dementia. SYNAPS Dx's laboratory is certified under the Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high complexity clinical laboratory testing. Physicians and patients seeking more information can visit https://discerntest.com/. For more information on the Company, visit https://www.synapsdx.com/. Contact: info@synapsdx.com.

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