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

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Part II.

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A Pathway Forward for Accurate Diagnosis and Treatment

Diagnosis and Misdiagnosis

Current AD diagnostic approaches may be inaccurate, especially in early stages of the disease and with mixed dementia. By placing focus on surrogate markers that are related to AD but not the disease itself, the distinction of AD can be difficult, especially in the presence of mixed cause dementia. In autopsy studies, over half of patients diagnosed with AD also had other causes of dementia occurring simultaneously, most commonly vascular and Lewy body dementias.[i] An earlier diagnosis, prior to dementia, can be even more challenging because most patients never progress to AD or dementia.

Approximately 25% to 30% of patients with a clinical diagnosis of AD dementia are misdiagnosed when assessed at specialized dementia clinics[ii], and the accuracy of clinical diagnosis is similar or even lower for other dementias, including frontotemporal dementia (FTD; an uncommon type of dementia that causes problems with behavior and language), dementia with Lewy bodies (DLB; impacts chemicals in the brain whose changes, in turn, can lead to problems with thinking, movement, behavior and mood) and vascular dementia (problems with reasoning, planning, judgment, memory and other thought processes caused by brain damage from impaired blood flow to your brain such as post-stroke.)

Clinical criteria provide a greater than 90% sensitivity for diagnosing dementia of any type, including AD, in a specialized clinical setting such as a memory disorders clinic.[iii] But they have a specificity of less than 70% for the actual diagnosis of AD, a factor which impacts most patients with cognitive or behavioral symptoms and are managed in primary care where the misdiagnosis is even higher.[iv] Fifty percent to 70% of symptomatic patients with AD are not recognized or correctly diagnosed in primary care today, because routine cognitive screening is not performed and there is a lack of easily accessible, time- and cost-effective and accurate diagnostic tools.[v] The problem is even worse in early stages of the disease in patients without dementia who have either subjective cognitive decline (SCD) or MCI.

Misdiagnosis leads to unnecessary care-seeking and costly investigations due to diagnostic uncertainty. In the early stages of AD, it is common for the symptoms to be misdiagnosed with a number of other medical issues that can bring on memory loss, such as Lyme disease, vitamin deficiencies, thyroid issues, drug interactions and various forms of dementia. This can cause a delay in detecting the presence of AD. In fact, 1 in 5 AD cases or 35,000 cases a year in the US may be misdiagnosed.[vi] In one recently reported instance, a patient was incorrectly diagnosed and treated for AD for seven years, which he said destroyed his life.[vii]

Clearly, clinicians, payers and patients need better tools to accurately identify AD in people recently diagnosed with dementia, even when the dementia is caused by several factors.

Accumulation of Amyloid Plaques in the Brain Influences AD in Living Patients

Research from the National Institute on Aging continues to help all stakeholders better understand how the accumulation of amyloid plaques in the brain influences AD in living patients, and at what stage.[viii] Many molecular and cellular changes take place in the brain of a person with AD. These changes can be observed in brain tissue under the microscope after death. Investigations are underway to determine which changes may cause AD and which may be a result of the disease.

Amyloid plaques

The beta-amyloid protein involved in AD comes in several different molecular forms that collect between neurons. In the Alzheimer's brain, abnormal levels of this naturally occurring protein clump together to form plaques that collect between neurons and disrupt cell function. Research is ongoing to better understand how, and at what stage of the disease, the various forms of beta-amyloid influence AD.

Neurofibrillary tangles

Neurofibrillary tangles are abnormal accumulations of a protein called tau that collect inside neurons. In AD, abnormal chemical changes cause tau to detach from microtubules and stick to other tau molecules, forming threads that eventually join to form tangles inside neurons. These tangles block the neuron's transport system, which harms the synaptic communication between neurons.

Promising New Drugs Pose Significant Safety Challenges

With the anticipated approval of new drugs, payers and healthcare providers are beginning to rely upon the DISCERN test for the most accurate diagnosis and to ensure that treatment is optimized for appropriate patients. Uncertainties regarding how to best diagnose AD persist despite the ongoing development and introduction of drugs to treat AD. These treatments have shown modest efficacy in slowing progression of cognitive decline but have significant safety considerations.

Aduhelm™ (Aducanumab)

In June 2021, the U.S. Food and Drug Administration (FDA) granted accelerated approval for Aduhelm as the first indicated for AD disease treatment to address a defining pathology of the disease.

Despite original approval of Aduhelm, developed by Biogen, the federal Centers for Medicare & Medicaid Services (CMS) announced in 2022 that it refused to cover Aduhelm under Medicare unless it was part of a clinical trial, arguing that the drug's efficacy hasn't been adequately demonstrated and that questions about its safety remain unanswered. A statement said, "The FDA's approval of Aduhelm raised concerns due to alleged scientific disputes within the FDA, the advisory committee's vote against approval, allegations of an inappropriately close relationship between the FDA and the industry, and the FDA's use of the accelerated approval pathway."[ix]

Overview: Centers for Medicare & Medicaid Services (CMS) Coverage

A complete review of CMS coverage criteria may be found here.

CMS proposes to cover FDA approved monoclonal antibodies directed against amyloid for the treatment of AD under Coverage with Evidence Development (CED) in CMS approved randomized controlled trials that include patients with a clinical diagnosis of mild cognitive impairment (MCI) due to AD or mild AD dementia; and evidence of amyloid pathology consistent with AD.[x]

Moreover, the diversity of patients included in each trial must be representative of the national population diagnosed with AD.

If these new amyloid targeting drugs for AD are approved and reimbursed, the CMS guidance for Aduhelm may serve as a benchmark for access, requiring among other things, the (i) presence of amyloid plaque consistent with AD, and (ii) MCI due to AD or AD dementia. Although the combination of blood biomarkers and imaging may be sufficient to address the presence of amyloid consistent with AD, they fall short in providing a definitive diagnosis of AD dementia or MCI due to AD.

Lecanemab

Pharmaceutical companies Biogen and Eisai announced initially encouraging results from a clinical trial for patients with AD: a monoclonal antibody treatment, lecanemab, which reportedly reduced cognitive decline by 27% in people with early-stage AD compared with those on a placebo after a year and a half and was FDA approved in early 2023.[xi] Outside observers say the trial could offer hope to some of the millions of people afflicted worldwide, who are largely bereft of treatments. The drug lecanemab is a monoclonal antibody designed to clear clumps of protein from the brain that many think are a root cause of AD.

Complications from amyloid-related imaging abnormalities (ARIA) associated with the investigational use of monoclonal antibodies targeting Aβ, including aducanumab and lecanemab, in patients with AD have been controversial in the past. Of concern is that once this drug gets into a much broader population, one more diverse from a baseline health perspective with limited or inconsistent access to brain imaging, the incidence of significant adverse events (AEs) may increase. Moreover, in well controlled clinical trials the rate of ARIA was 20% vs 3% for placebo. As safety issues often increase once a drug is used in practice, especially in older patients, the implications of ARIA on patient mortality and morbidity may be hard to assess from the clinical trials and increased monitoring with brain imaging may be required.[xii]

In addition to pharmacological interventions to slow cognitive decline due to AD, additional NIH and NIA funded research is ongoing to evaluate the role of lifestyle modification on cognitive decline. Data presented at the 2022 Clinical Trials on Alzheimer's Disease (CTAD) meeting from the SMAART study[xiii] suggests that weekly counseling that addresses known modifiable risk factors, such as uncontrolled diabetes, smoking and hypertension can reduce cognitive decline and improve quality of life in people with MCI. Additional data presented from the EXERT trial (Baker et al OC12) demonstrated that even modest exercise reduced cognitive decline in people living with MCI over 12 months. While more studies are warranted, these data suggest that lifestyle modification may play an important role in managing early AD, either in combination or as step therapy prior to initiating pharmacological intervention.

Challenges to Payers

The nation's payers, including commercial, Medicare Advantage, Managed Medicaid and dual eligible plans will be challenged to set prescribing guidelines for these drugs to ensure that they are recommended for the most appropriate patients. New diagnostic criteria for AD and MCI incorporate updated scientific insights and technological advances.[xiv] The new guidelines aim to improve current diagnosis, strengthen autopsy reporting of brain changes and establish a research agenda for future progress in earlier detection and even greater diagnostic accuracy.

Three of the guidelines for research focus on three stages of AD include: (1) dementia due to AD, (2) MCI due to AD, and (3) preclinical (presymptomatic) AD. The fourth guideline updates criteria for documenting and reporting AD-related changes observed during an autopsy.

The final and complete version of the guidelines, revised to reflect input from the professional community at large, now appear as free-access papers in Alzheimer's & Dementia®: The Journal of the Alzheimer's Association.

These guidelines point to the importance of making an accurate diagnosis, early in the disease pathway. Once approved, these new drugs place clinicians and payers in a difficult position: patients and families will demand the drug, sometimes at any cost, and payers will seek to limit access to only those who will likely benefit the most. It is anticipated that the DISCERN test will inform a definitive diagnosis of AD in patients recently diagnosed with dementia or living with mixed dementia, bringing clarity for prescribing recommendations coverage, prior authorizations and co-pays.

In addition to the cost of the drug itself, there are other significant expenses, including the fees associated with administration: one or two, one-hour infusions every month.

Lecanemab: Infusions every two weeks
Aduhelm: Studies recommend once per month
Donanemab: Currently studied as a monthly infusion
Monitoring for ARIA: MRI imaging was performed seven times during the 18-month aduhelm study.[xvi]

Introducing the DISCERN Test

Given the myriad of issues surrounding the market entry of new drugs and potential limitations of BBMs as diagnostic tools for diagnosing AD itself, a promising breakthrough for identifying AD is the DISCERN test. Unlike the BBMs, DISCERN is an autopsy-confirmed, minimally invasive skin test to support clinicians' definitive diagnoses of AD vs. other forms of dementia—the first test to identify and distinguish AD, based on autopsy-validation, from non-AD dementia. This test has the potential to help patients and families get the right support or treatment path for improved quality of life.

Over a decade of research has discovered that AD pathology can be observed in peripheral tissues such as skin, introducing a new target for disease-related biomarkers. Studies have shown that Aβ can form deposits in the skin of AD patients. These reinforce the discoveries by SYNAPS Dx (SDx) that led to the development of the DISCERN test, which reliably and accurately identifies neurological changes associated with AD from a simple skin biopsy.

SDx developed DISCERN to provide healthcare professionals a test to identify and distinguish AD in people recently diagnosed with dementia, even in the presence of co-morbid pathologies. DISCERN has been autopsy validated to identify AD against the NIH Gold Standard of dementia in life and plaque and tau at death.

DISCERN, a Laboratory Developed Test (LDT) is the first of its kind to earn Proprietary Laboratory Analyses (PLA) Codes 206U and 207U by the American Medical Association (AMA) and gap-fill status by CMS (Medicare). The DISCERN test was granted Breakthrough Device designation by the FDA and has Clinical Laboratory Improvement Act (CLIA) status for 49 of 50 states.

The test is comprised of three assays (Morphometric Imaging [MI], PKC ε, and AD-Index) performed on a single skin punch biopsy. The MI assay was able to effectively diagnose AD in a minimally invasive manner on a living patient with greater than 95% accuracy, specificity and sensitivity overall. Values between all parameters did not overlap between AD and non-AD patients, demonstrating the ability to distinguish between AD and other forms of dementia. Early stages of AD can be accurately diagnosed with the MI assay.

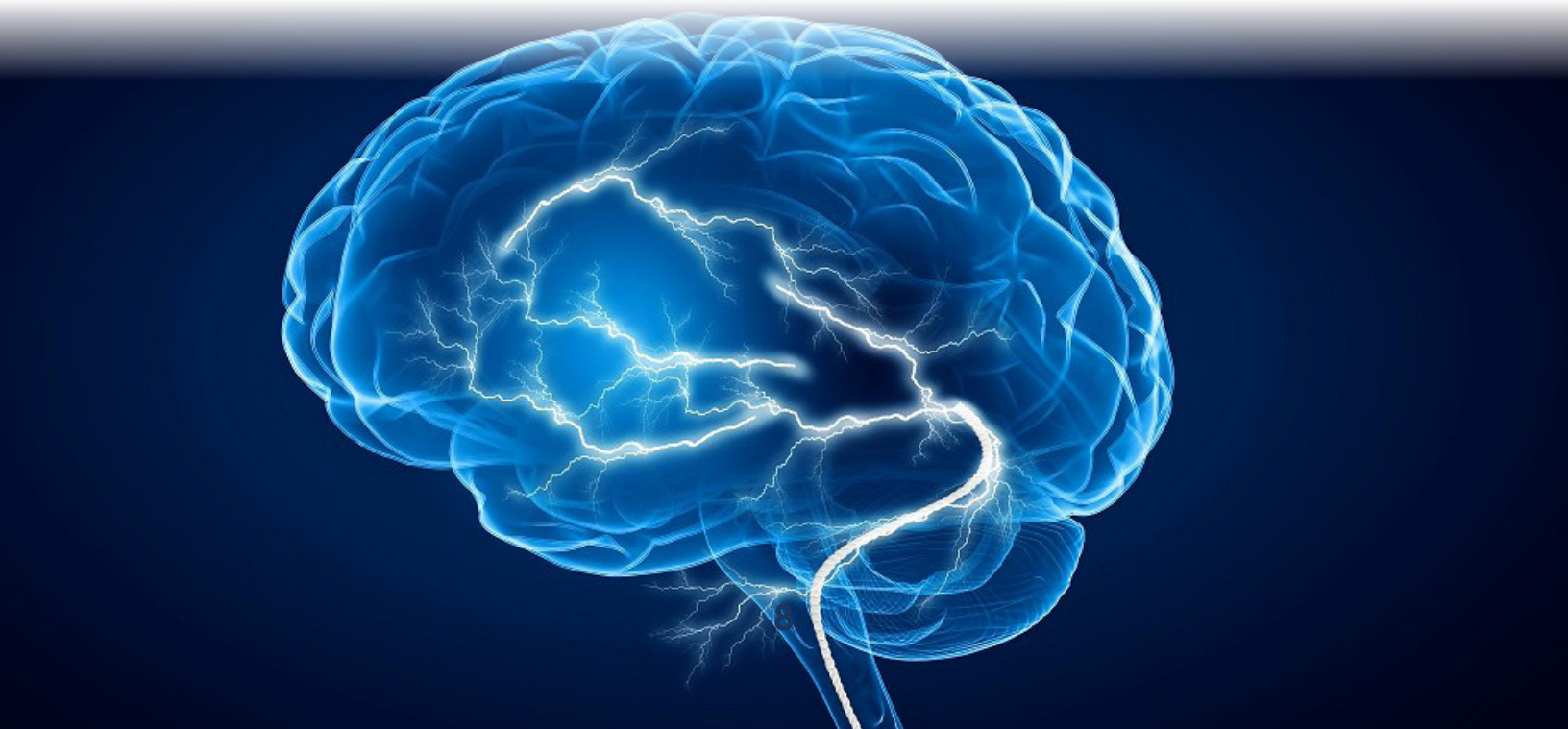
The DISCERN test provides a substantial advantage over other biomarker tests by detecting AD once diagnosed with dementia, even in the presence of mixed-dementia. The MI Assay includes preclinical stages, providing a longer window of time for medical interventions that can improve patient prognosis. Results from MI analysis allow patients to improve the regimen of therapeutic interventions to help prevent cognitive decline earlier in the disease process.

Key Benefits of the DISCERN Test

- Simple, minimally invasive and definitive screening diagnostic for AD in a living patient.
- High sensitivity and specificity of results correlating with postmortem diagnosis based on autopsy validation.
- Diagnostically distinguishes AD from other forms of dementia.
- Able to diagnose AD in mixed co-morbid state with other types of dementia.
- Early detection of AD enables swift therapeutic intervention to prevent cognitive decline.

Prior to the introduction of the DISCERN test, there have been no autopsy-validated tests shown to accurately identify AD in the presence of mixed dementia, or dementia from one or more co-existing causes, which affect over half of patients diagnosed with AD. By utilizing the DISCERN test, clinicians and patients can avoid unnecessary, invasive and expensive diagnostic procedures conventionally used to diagnose AD in people with dementia. DISCERN is autopsy-validated to inform a definitive diagnosis of AD in people with dementia by assessing several factors related to synaptic and neuronal loss that impact cognitive loss, as well as regulators of amyloid plaque and neurofibrillary tangles in the brain.

While DISCERN is not intended to provide a complete answer for identifying the appropriate patient, it does uniquely provide greater certainty around the determination of AD in people recently diagnosed with dementia, even in the presence of mixed dementia. With use of the DISCERN test, which relates to loss of synaptic networks as well as amyloid and tau, clinicians will have greater confidence in the diagnosis of AD and identifying patients with AD dementia who are appropriate candidates for treatment.



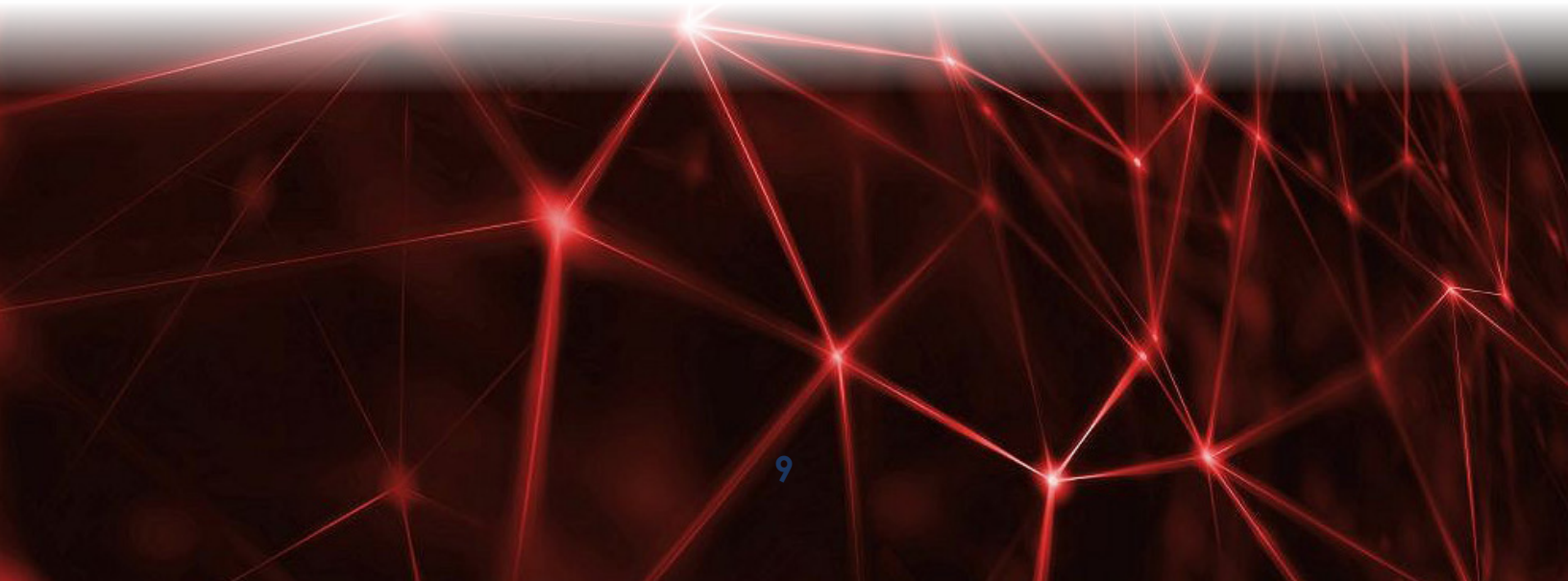
A Bright Horizon

Linking the behavioral and neurological symptoms of AD with the frequently associated pathology of amyloid plaques and neurofibrillary tangles has spawned the "amyloid cascade hypothesis"—a vision of the etiology of AD that spurred the discovery of many important insights into the neurobiology of the disease.[xix]

Despite these successes, the wealth of new data now available to biomedical researchers urges a full review of the origins of AD and the need for a reconsideration. Increasingly it is recognized that amyloid cascade hypothesis may be a part of the solution to AD. "Reimagining Alzheimer's Disease—An Age-Based Hypothesis" authored by Karl Herrup begins with the most widely accepted risk factor for developing AD: age.[xx] Then, for an individual to progress from normal age-appropriate cognitive function to a condition where the full palette of clinical symptoms is expressed, three key steps are envisioned: **(1) an initiating injury, (2) a chronic neuroinflammatory response, and (3) a discontinuous cellular change of state involving most, if not all, of the cell types of the brain.**

Herrup asserts that the pathology of amyloid plaques is envisioned as highly correlated with, but mechanistically distinct from, the three obligatory steps leading to AD. Thus, there are uncertainties about the amyloid cascade hypothesis.

Over time, growing amounts of data have accumulated that are inconsistent with the linear structure of this hypothesis. While there is fear in the field over the consequences of rejecting it outright, clinging to an inaccurate disease model is the option that should create concern. Many industry observers are now exploring the proposition that healthcare decision-makers are over-reliant on amyloid to define and diagnose AD and that the time has come to face these doubts and reject the amyloid cascade hypothesis.



Given this backdrop of uncertainty, especially around the role of BBMs in identifying the presence of amyloid, but not a diagnosis for AD, it is reassuring to see data being released that provides greater understanding of AD prevalence. For example, recently released data in JAMA Neurology results from a national study of AD prevalence showed that almost 10% of Americans over 65 have dementia and 22% have mild cognitive impairment. Data from the Alzheimer's Association shows 27% of Americans between ages 65 and 74 have AD while the prevalence increases to 35.7% in those 85 and older.[xxii]

The study, based on 3,500 people enrolled in the longitudinal Health and Retirement Study who received comprehensive neuropsychological tests, found that 9% of white people, 10% of Hispanic people and 15% of Black people had dementia.[xxiii] Dementia affected 13% of those who had less than a high school degree, but just 9% of those with a college degree or more. The study found no differences in prevalence between males and females, consistent with other studies that account for longer longevity in females.[xxiv]

What is encouraging is the role of the DISCERN test and the ongoing dedication of researchers to provide a path forward for so many people. The years ahead will likely herald a wide range of solutions and interventions to halt the progression of AD and bring hope to millions of individuals and their families.

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.

RESOURCES

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