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Clinical Study of Novel Skin Biomarker Test for Alzheimer's Disease Gains Vigorous Physician Support in Long-Sought Early Detection Breakthrough

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Alzheimer's disease (AD) is a complex condition that weighs heavily on the global psyche. A 2018 survey found that 62% of respondents worry they will contract the disease.[i] In reality, about 10% of those over 65 will contract AD, but the odds jump to 50% after age 85.[ii]

Experts believe science has primarily focused on amyloid to accurately diagnose AD, when in reality, AD is a complex, neurodegenerative form of dementia that requires a more nuanced approach than the linear structure of current diagnostic pathways.[iii]

While the underlying cause of AD is still unknown, experts agree that changes in the brain due to age, combined with genetic, environmental and lifestyle factors all play an important role in disease progression.[iv]

Developing AD can be a frightening prospect: it is the most common form of dementia and the fifth cause of death in the U.S. for adults over 65.[v] AD is a brain disease caused by damage to neurons associated with memory, language and thinking. The condition is progressive, which means it gets worse over time.[vi]

Furthermore, the economic burden of AD is significant. In 2020, the cost of AD was $305 billion, a figure that is expected to increase to $1 trillion over time. Direct costs include skilled nursing home care, home health care and hospice care for patients with AD. Indirect costs include informal caregiving by family and a decline in quality of life for patients and caregivers.

Mild Cognitive Impairment

A key market changer is the introduction of monoclonal antibodies to treat mild cognitive impairment (MCI) due to AD or AD dementia. To date, these drugs have demonstrated a slowing of progression, albeit with significant patient burden and safety considerations. Payers and physicians will come to readily recognize the names of Eisai's lecanemab and Eli Lilly's donanemab as anti-amyloid treatments for MCI due to AD and AD dementia. Some of which will gain FDA approval and be heavily marketed to providers, payers and patients with MCI due to AD or AD dementia. These treatments are expected to fare better in the market than Biogen's aducanumab, which was controversially approved in 2021.

Another daunting fact is that the number of Americans with AD is projected double by 2050, leaving physicians burdened with how to manage the condition of a growing number of patients. Nine in 10 primary care physicians expect to see an increase in people living with dementia by 2025.[vii] Significantly, half of physicians report that the medical profession is unprepared for such demand. Yet, the survey also revealed that 92% of patients and caregivers expect their primary care physician to "know the latest thinking and best practices around dementia diagnosis and care."[viii]

It is recognized that earlier intervention may delay disease progression for many patients. MCI, the stage at which a patient first begins suffering from a decline in concentration, communication, memory or orientation, has been identified as an opportunity to intervene with disease modifying drugs. The challenge is how to identify patients with MCI who will progress to dementia.

As an early stage of memory or other cognitive ability loss, people living with MCI experience cognitive changes, but these may not be significant enough to impact an individual's activities of daily living.[ix] Prevalence of MCI rises with age as studies show 6.7% of people aged 60-64 experience MCI, rising to 25.2% for people aged 80-84.[x] However, it is important to note that studies show that less than half of people with MCI will progress to dementia, let alone AD dementia, within 10 years.[xi]

Risk factors for MCI include :

Increasing age

Having a specific form of the Apolipoprotein E gene (APOE-e4) that has been linked to AD

Some medical conditions and other factors, such as:

-Diabetes
-Smoking
-High blood pressure
-High cholesterol
-Obesity
-Depression
-Sedentary lifestyle
-Infrequent participation in mentally or socially stimulating activities.

Source: Alzheimer's Association; 2022 Alzheimer's Disease Facts and Figures; 2022; accessed Dec. 6, 2022.

Public awareness of MCI is low, with symptoms often mistaken for normal aspects of aging. Fewer than 18% of Americans are estimated to be familiar with MCI, even among people aged 60 or older, the population most likely to experience the disease.

Primary care physicians (PCPs) reported similar results with 13% indicating they feel patients understand MCI and 81% reporting patients believe MCI is part of aging. PCPs indicated they are not comfortable diagnosing MCI, with 35% reporting discomfort and 51% reporting discomfort diagnosing MCI due to AD. While almost all of those surveyed reported it is important to screen for MCI, only 48% reported doing so for their patients over 60 years old. Dissatisfaction is evident with 51% of PCPs reporting challenges such as lack of diagnostic tests, 49% reporting patient resistance and 47% citing limited treatment options. This is especially significant as 86% also reported early intervention of MCI can slow progression of cognitive decline.

A recent study by the Alzheimer's Association found that due to lack of easily accessible, time- and cost-effective accurate diagnostic tools, 50% to 70% of symptomatic patients with AD are not recognized or correctly diagnosed.[xiii] The study also shows the misdiagnosis rate is 25% to 30% in specialty memory care clinics.[xiv]

According to the National Institute on Aging, doctors use several methods and tools to help determine if a person with thinking or memory problems has AD. To diagnose Alzheimer's, doctors may:[xv]

- Ask the person experiencing symptoms, as well as a family member or friend, questions about overall health, use of prescription and over-the-counter medicines, diet, past medical problems, ability to carry out daily activities and changes in behavior and personality.[xvi]
- Administer a psychiatric evaluation to determine if depression or another mental health condition is causing or contributing to a person's symptoms.
- Conduct tests of memory, problem solving, attention, counting and language.
- Order standard medical tests that can help identify other possible causes of the problem or perform brain scans to support an AD diagnosis or rule out other possible causes for symptoms.[xvii]

But the availability of diagnostic tests is still limited, although research teams continue to study options for faster, less-expensive and less-invasive ways to diagnose AD. The only way to conclusively diagnose the disease is after death through a post-mortem autopsy. Another challenge is distinguishing AD from the other four types of common dementia (commonly referred to as mixed-dementia).[xviii] Studies show over 50% of people with AD also have other pathologies of dementia, further complicating the diagnostic process.[xix] However, according to the Alzheimer's Association, AD accounts for up to 80% of dementia cases.[xx]

Advancements in Treatment

As the world continues to evaluate the most effective diagnostic tools, the U.S. Food and Drug Administration (FDA) approved aducanumab (Aduhelm) in June 2021, based on the surrogate end point of reducing amyloid beta plaque in the brain.[xxi] Aduhelm is an amyloid beta-directed antibody indicated to treat AD and was approved under the accelerated approval pathway, which provides patients with a serious disease earlier access to drugs when there is an expectation of clinical benefit despite some uncertainty about the clinical benefit.[xxii]

However, the FDA's decision to approve the drug was widely criticized by researchers and clinicians.[xxiii] Many noted that the drug's approval ran counter to the recommendations of the FDA's Peripheral and Central Nervous System Drugs Advisory Committee of independent experts.

Less than a year later, however, the Centers for Medicare & Medicaid Services (CMS) announced that it will cover the controversial drug Aduhelm for the treatment of AD only if patients are enrolled in a qualifying clinical trial. Besides characterizing the evidence that aducanumab could slow cognitive decline in people in the early stages of the disease as unconvincing, the committee also noted that the drug, which is given as a monthly infusion, can cause potentially serious adverse effects, notably brain edema and brain hemorrhage.

This proposed CMS National Coverage Determination, which was finalized in April after a public comment period ending in mid-February, would sharply limit the number of patients with AD who could use the medication.[xxiv] The decision would also apply to similar monoclonal antibody–based drugs that target amyloid beta and are currently in clinical trials. The patient criteria includes a clinical diagnosis of MCI due to AD or mild AD dementia and demonstrated amyloid pathology consistent with AD without any other neurological or medical condition that contributes to cognitive decline, expected death from another cause during the study or other medical conditions that may increase adverse events. [xxv]

CMS Administrator Chiquita Brooks-LaSure, MPP, says, "CMS has proposed an evidence-based coverage policy after experts reviewed all relevant publicly available evidence and feedback received from stakeholders."[xxvi]

Luhby, T; Medicare proposes to cover controversial Alzheimer's drug with restrictions; Jan. 11, 2022; accessed Dec. 6, 2022.

Reports in the media noted that the decision appears to be the first time that CMS has restricted access by Medicare beneficiaries to a drug approved by the FDA.[xxvii,xxviiii]

According to the findings of a global survey (France, Germany, Japan, the U.K. and the U.S.), caregivers were the main driver of an AD diagnosis.[xxix] Physician suspicion of the disease factored only into about 20% of diagnosed patients.

Such caregiver burden is well documented. For example, a 2017 study noted that the emotional burden and psychological distress for family members who act as caregivers for those with AD are as severe as the economic burden.[xxx] As the disease progresses, the caregiver burden intensifies. Understandably, caregivers feel despair and weariness. Loneliness contributes to a decrease in the quality of life and body physiology. The study authors note that:

> "Since there is no treatment option to heal AD or stop its progress, presently, the goal should be to improve and support the quality of life for patients, their families, and their caregivers as much as possible… The process of providing care to an AD patient is toilsome in many ways, and it shapes not only the life of the patient but also the lives of their families and caregivers…"

Koca, E., Taşkapilioğlu, Ö., & Bakar, M. (2017). Caregiver Burden in Different Stages of Alzheimer's Disease. Noro psikiyatri arsivi, 54(1), 82–86. https://doi.org/10.5152/npa.2017.11304

Racial Disparities

The Alzheimer's Association reports that racial and ethnic disparities in health and health care, such as those observed during the pandemic, extend to dementia care.[xxxi,xxxii] They point to such issues as stigma, cultural differences, awareness and understanding, along with the compromised ability to obtain a diagnosis, manage the disease and access care and support services for dementia. These factors vary widely depending on race, ethnicity, geography and socioeconomic status. Equally troubling is that these disparities reach beyond clinical care to include uneven representation of Black, Hispanic, Asian and Native Americans in AD research in clinical trials.

Further confirmation of these challenges emanates from USAgainstAlzheimer's, founded in 2010 to disrupt and diversify the movement to cure AD.[xxxiii] It projects that by 2030, nearly 40% of all Americans living with AD will be Black or Latino, with Black Americans twice as likely than non-Hispanic Whites to develop AD and Latinos 1.5 times as likely.

According to AfricanAmericansAgainstAlzheimer's, a network of USAgainstAlzheimer's and the nation's first organization dedicated to building a coordinated national response to eliminate and address AD among African Americans, AD is the fourth leading cause of death for older African Americans and has a disparate impact on African Americans. The organization reports that African Americans are two to three times more likely to develop AD than white Americans, yet they are less likely to be diagnosed. They point to participation in clinical trials as a critical factor in finding a cure for AD and assert that while African Americans make up over 13% of the population, they are only five percent of clinical trials participants. This number is even lower for older African Americans.

Here is the prevalence data according to the Alzheimer's Association: "Older Black and Hispanic Americans are also disproportionately more likely to have AD and other dementias, as well as more likely to have missed diagnoses, than older White Americans.

Caregiving for individuals with AD or other dementias differs between racial and ethnic groups too. These differences include the availability of support services, the time spent on caregiving, cultural perceptions of the burden of caregiving, whether social networks provide support and the psychological well-being of the caregiver."

Alzheimer's Association. Special Report. Race, Ethnicity and Alzheimer's in America, 2021. https://www.alz.org/media/Documents/alzheimers-facts-and-figures-special-report-2021.pdf

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Given these statistics, the Alzheimer's Association conducted Adult and Caregiver Surveys to better understand racial and ethnic attitudes and experiences regarding AD and dementia care in the United States. It "commissioned Versta Research to conduct surveys of (1) U.S. adults and (2) current or recent caregivers of adults age 50 or older with cognitive issues. Respondents were asked about access to care and support services, trust in providers and the health care system, participation in clinical trials and research and caregiver experiences.

This is the first Alzheimer's Association survey to ask and report the views of Asian Americans and Native Americans on these issues. It is also one of the few reports to investigate the experiences of diverse caregivers. Key survey findings revealed: discrimination is a barrier to AD and dementia care."

- More than one-third of Black Americans (36%), and nearly one-fifth of Hispanic Americans (18%) and Asian Americans (19%), believe discrimination would be a barrier to receiving AD care.

- Half of Black Americans (50%) report they have experienced health care discrimination; more than 2 in 5 Native Americans (42%) and one-third of Asian Americans (34%) and Hispanic Americans (33%) likewise report having experienced discrimination when seeking health care.

- Among non-White caregivers, half or more say they have faced discrimination when navigating health care settings for their care recipient, with the top concern being that providers or staff do not listen to what they are saying because of their race, color or ethnicity. This concern was especially high among Black caregivers (42%), followed by Native American (31%), Asian American (30%) and Hispanic (28%) caregivers. Fewer than 1 in 5 White caregivers (17%) expressed this view.

- Two in 5 caregivers (41%) who provide unpaid care to a Black person say that race makes it harder for them to get excellent health care. Nearly 1 in 3 caregivers of Hispanic people (32%) say the same.

Alzheimer's Association. Special Report. Race, Ethnicity and Alzheimer's in America, 2021. https://www.alz.org/media/Documents/alzheimers-facts-and-figures-special-report-2021.pdf

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In light of this information and survey findings, it is critical that that these marginalized populations have access to accurate diagnostics, clinical trial participation, care and treatment. The toll of AD on these communities is severe.

Inadequate Diagnostic Protocols

These issues point to the inadequate state of the current standard protocols to diagnose AD. According to the Alzheimer's Association, a cognitive assessment can help with an early diagnosis, but there is some frustration with current AD diagnostic effectiveness.[xxxiv]

It is important to note that new data available to biomedical researchers indicates that previous associations between the presence of amyloid and AD may need to be reconsidered.[xxxv] Researchers now believe 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 occur: (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.

"Blood biomarkers (BBMs) have been proposed as minimally-invasive, easily accessible, globally scalable and cost-effective triaging tests to be used early in the diagnostic pathway before confirmation of AD pathology via CSF or PET testing. BBMs have the potential to increase the efficiency of the AD diagnostic pathway by fast-tracking people with expected underlying AD pathology to a timely confirmation of amyloid pathology via CSF or PET which is a prerequisite for anti-amyloid therapy administration. To date, the vast majority of data on BBMs has been generated using retrospectively measured banked blood samples collected in well-controlled study settings in populations of European descent. Using banked samples is usually the first logical step in assessing the diagnostic value of newly discovered biomarkers. However, it can have major limitations in translatability to a real-world setting."[xxxvi]

Bittner, T. What Are the Remaining Challenges before Blood-Based Biomarkers for Alzheimer's Disease Can Be Used in Clinical Practice?. J Prev Alzheimers Dis 9, 567–568 (2022). https://doi.org/10.14283/jpad.2022.89

While there is increased examination of the role of using blood biomarkers for AD diagnosis outside of clinical trials, there is widespread concern on whether these should be used with caution, as suggested by the NIH and the Alzheimer's Association. Many are questioning the wisdom of offering these tests as part of "real-world" evidence studies in advance of the availability of effective treatments that are not connected to clinical research for people living with cognitive impairment.

Given the lower sensitivity of the screening test and the high variability of progression from MCI to dementia, this approach may have the unintended consequences of confusion and frustration among patients and their families. Moreover, as noted by the Association, resources for the necessary confirmatory tests, such as advanced imaging technologies may not be readily accessible to these communities. In fact, the Association offers this guidance that blood biomarkers for AD should be used "cautiously in specialized memory clinics as part of the diagnostic work-up of patients with cognitive symptoms and the results should be confirmed whenever possible with CSF or PET." [xxxvii]

Most recently, the Alzheimer's Association 2022 Alzheimer's Disease Facts and Figures report unearthed new insights related to challenges both doctors and the American public face in understanding and diagnosing MCI, which is characterized by subtle changes in memory and thinking.[xxxviii] The report estimates that 12% to 18% of people age 60 or older have MCI. While some individuals with MCI revert to normal cognition or remain stable, studies suggest as many as 10% to 15% of those individuals with MCI go on to develop dementia each year. As the size of the U.S. population age 65 and older continues to grow (from 58 million in 2021 to 88 million by 2050), so too will the number and proportion of Americans with AD or other dementias given increased risk of dementia with advancing age.

Identifying which individuals living with MCI are more likely to develop dementia is a major goal of current research, potentially enabling earlier disease intervention and treatment.

Perhaps one of the most compelling studies, "The Challenges of Diagnosis in Alzheimer's Disease," puts a finer point on the need for a better protocol to diagnose AD:

"There is, therefore, a need for biomarkers related to pathological changes, as well as new imaging approaches that can detect the early stages of A.D. Understanding the patient's disease stage is very important for prognosis, treatment and appropriate recruitment into clinical trials. Some recent clinical trials may have failed because the patients had an advanced form of the disease or were misdiagnosed (lacking amyloid as a target) and therefore promising antibodies were likely to be 'ineffective.'"[xxxix]

Bogdanovic, Nenad. (2018). The Challenges of Diagnosis in Alzheimer's Disease. European Neurological Review. 14. 15-16. 10.17925/USN.2018.14.1.15.

A Recent Advancement in Early, Accurate Detection

One of the most remarkable advances is the DISCERN test, which is currently available to inform a definitive AD diagnosis in people recently diagnosed with dementia and identifying AD, even when other forms of dementia are present. Such early clinal insight is vital to improving patient outcomes, helping patients and caregivers proceed to lifestyle planning (safety risks), prevention of complications and managing access with approved modifying therapies/costs.

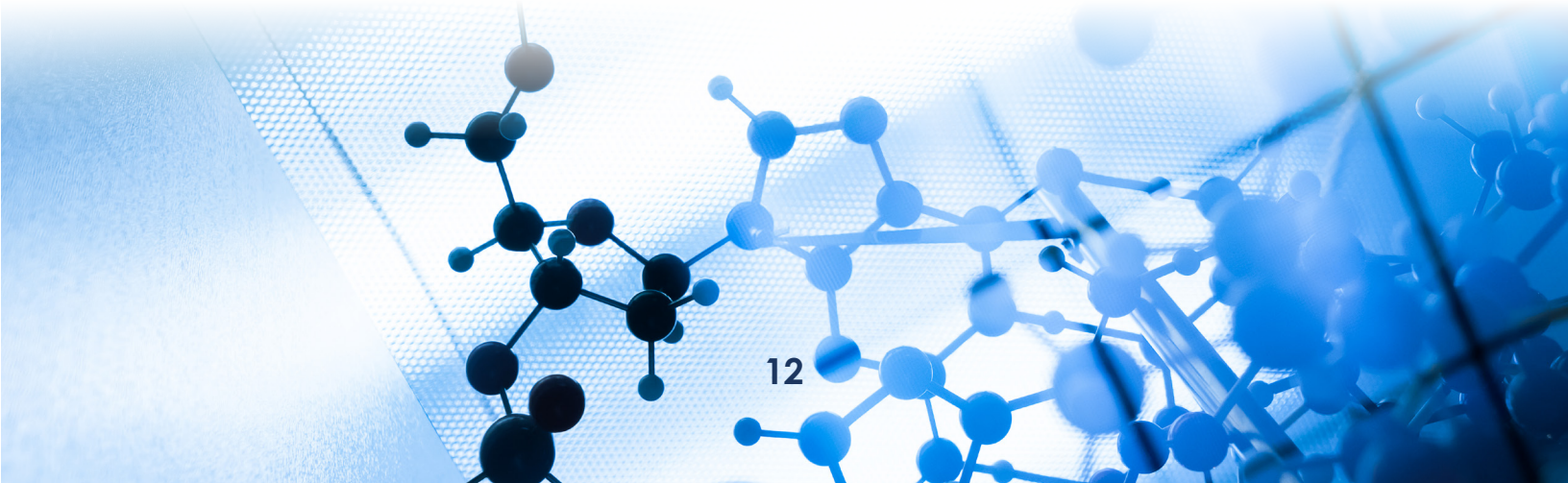
The three DISCERN biomarkers assess several critical factors directly related to AD that regulate memory, the formation of synaptic connections among neurons, the levels of amyloid plaques and levels of neurofibrillary tangles in the brain. The test requires only a small skin sample to analyze the biomarkers, which consist of:

- **Morphometric Imaging (MI):** In a clinical trial with the MI Assay, patients with autopsy-confirmed AD could be accurately distinguished from patients with non-AD dementia and age-matched controls with 100% sensitivity and specificity.

- **PKCε Assay:** In a clinical trial with the PKCε Assay, patients with autopsy-confirmed AD could be accurately distinguished from patients with non-AD dementia and age matched-controls with 100% sensitivity and 96% specificity.

- **AD-Index:** In a clinical trial with AD-Index Assay, patients with autopsy-confirmed AD could be accurately distinguished from patients with non-AD dementias and age-matched controls with 97% sensitivity and 94% specificity.

The utility of having a test that informs a definitive diagnosis of AD has been validated by physician research in a recently published study.[xl] A total of 402 physicians (50 geriatricians, 102 neurologists and 250 PCPS) participated in the study.



The study concluded:

> "The DISCERN test addresses several unmet needs identified in AD diagnosis and management. The results from our study indicate that physicians see value in the information from the DISCERN test and would order the information from the DISCERN tests to make clinical decisions compared to current SOC tests. This study provides evidence demonstrating the clinical utility of the DISCERN test and has implications for clinicians (stet) adopting the test and payers evaluating coverage of the test."

Samson C, Mark N, Datar M, Howell S, Huie F, Goss TF; Physicians' Assessment of the Clinical Utility of a Novel Test to Diagnose Alzheimer's Disease (AD); n.d.; accessed Dec. 6, 2022.

DISCERN also provides economic benefits. A three-year economic projection presented at the International Conference on Aging Diseases and Elderly Care (ICADEC) in December outlines a projected $4.75 million in savings in the care of Medicare Advantage patients.[xli] The amount was totaled from a cohort of patients tracked over three years, with an individual covered life savings of $63.11 per member. The study concludes that DISCERN diagnosed AD earlier in the disease stage and may generate savings for Medicare Advantage plans.

On the Horizon

In the volatile diagnostic and treatment environments, AD diagnoses often cause physician anxiety, placing doctors between patients, family members and caregivers looking for access and coverage for new treatments and payers waiting for data and more evidence of efficacy. Having a tool to identify appropriate patients will help clinicians find suitable patients who will benefit from these new drugs and maintain balance between patients and payers.

In many instances, primary care physicians are the first line of defense against AD and other forms of dementia. Just as they screen patients for cholesterol levels and blood pressure as part of basic preventative care, they are also being tasked to include memory screenings in their patients' diagnostic work-ups.

Keeping in mind that Medicare requires that patients receive a screening under its Cognitive Assessment and Care Plan, it is surprising to learn that fewer than half of primary care doctors in a survey report they routinely test patients 65 and older for memory challenges and fewer than 16% of patients report receiving a cognitive screening from their PCP.[xlii,xliii] Consider this data in comparison to the 91% who report they are screened for cholesterol levels and 83% who report undergoing a cholesterol test.

Despite these challenges, physicians are optimistic. A recent Harris Poll found that 65% of U.S. physicians believe that researchers are on the verge of an AD treatment breakthrough.[xliv] This may be wishful thinking since over a decade and billions of dollars have already been spent on research to find a cure for AD, yet none have thus far proved real clinical benefit.[xlv] If the elusive AD treatment isn't found soon, scientists estimate that by 2050 someone in the U.S. will develop the disease every 33 seconds.

Despite the many failed drug trials, many say the horizon is finally looking optimistic and multiple treatments are expected to be approved within the next few years.

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* The DISCERN™ test was developed and its performance characteristics determined by NeuroDiagnostics Inc, dba Synaps Dx. It has not been cleared or approved by the U.S. Food and Drug Administration. NeuroDiagnostics, Inc. is regulated under the Clinical Laboratory Improvement Amendments (CLIA) as an accredited laboratory to perform high complexity clinical testing. The test is intended for patients with dementia. Test results should be interpreted in conjunction with other laboratory and clinical data available to the clinician.

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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