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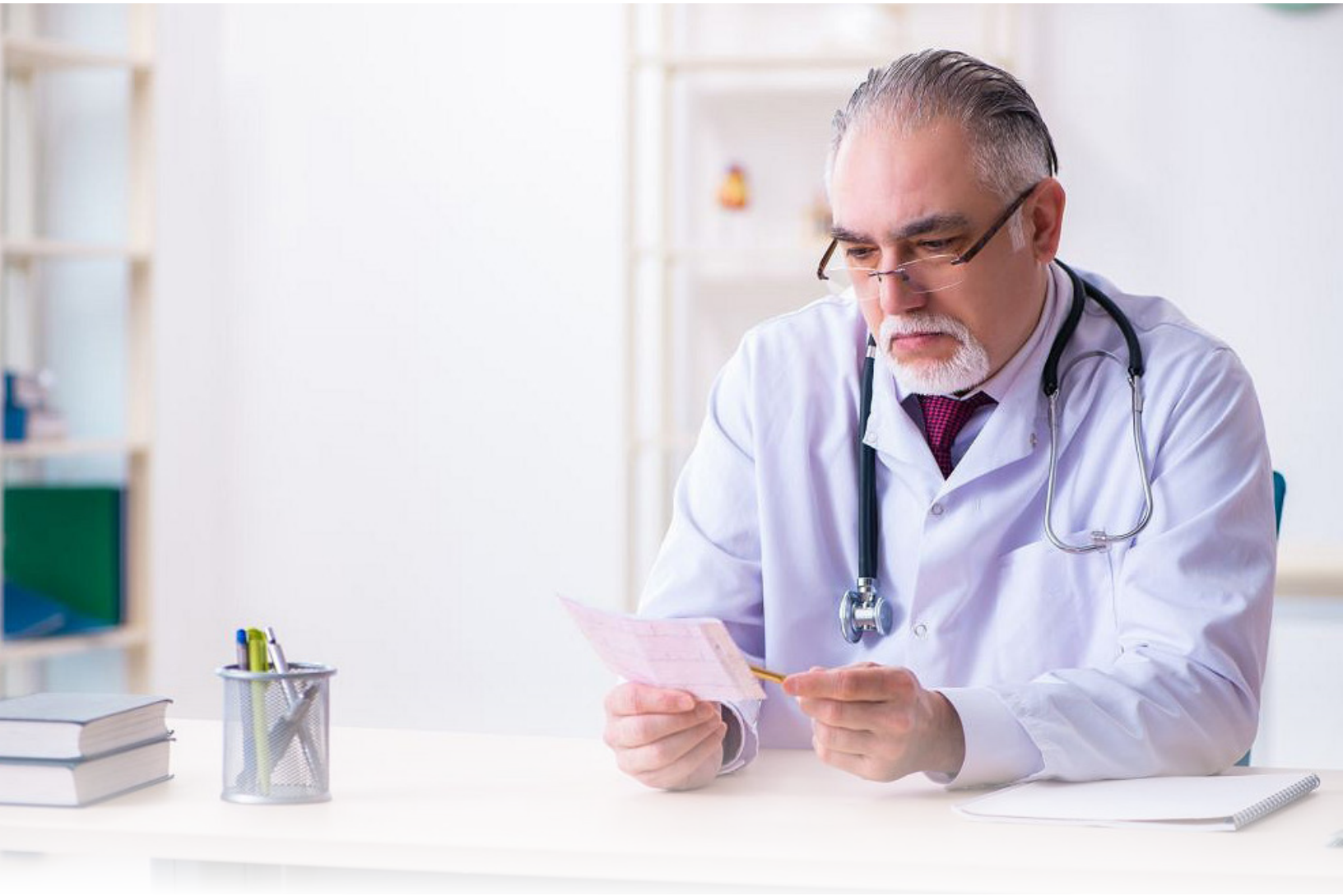

Resolving a Diagnostic Dilemma

By Frederick Huie, MD, Medical Director, CVS/Aetna and Advisory Council Member, SYNAPS Dx
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On the backdrop of a heated, very public debate regarding CMS coverage determinations and restricted patient access to new drugs to treat Alzheimer's Disease (AD), there is little to no discussion about the real questions that will face most people suffering from cognitive decline: **who is the right candidate for the drug and what other options are available to manage mild cognitive impairment (MCI) and AD dementia for those who are not candidates?**

What is really at stake in this discussion about treatment is the failure of this dialogue to address a sequence of unmet medical needs, including:

- Improving the accuracy of community-based AD diagnostics
- Enhancing the quality of specialist referrals
- Coordinating appropriate downstream testing such as costly imaging, invasive cerebrospinal fluid (CSF) puncture and expensive interventions
- Introducing diagnostic testing that can reduce costs, improve outcomes and increase patient satisfaction

With the potential introduction of new AD treatments and an aging population, now is the time to address the need for a simplified, validated and accurate diagnostic that is

According to the World Health Organization (WHO), the world's population of people 60 years and older will double by 2050.[1] The Alzheimer's Society states that age is the biggest risk factor for developing dementia. It is estimated that in the United States there are currently more than 6 million people living with AD. By 2050, this number is projected to rise to almost 13 million.[2] In the near future, we will have substantially higher numbers of people diagnosed with dementia and AD. Even more concerning, there will be larger numbers of symptomatic people who will be misdiagnosed with AD due to the inaccuracies in current diagnostic tests.

Implementation of a diagnostic pathway to accurately diagnose AD, broadly defined as the route that patients take from first presenting with symptoms to a clinician to receiving an accurate diagnosis, is woefully inadequate. People who visit their general practitioner with vague symptoms often do not meet the criteria to be referred for tests and so can experience long delays before they are diagnosed.

Even more troubling, the Alzheimer's Association reports that in the community setting, **50-70% of symptomatic patients are incorrectly diagnosed with AD and that number is reduced to 25%-30% misdiagnosed in specialized memory clinics.** The Association faults the inconsistency of routine cognitive screening and the lack of easily accessible, accurate and time- and cost- effective diagnostic tools.[3]

This diagnostic conundrum is even worse in early stages of the disease, impacting patients without dementia who have either subjective cognitive decline (SCD) or mild cognitive impairment (MCI).[4] Unfortunately, cognitive tests currently available for primary care settings are inadequate to differentiate SCD and MCI.[5]

Making the Diagnosis: Is it AD or Dementia?

There is widespread misunderstanding and confusion about the difference between AD and dementia.[6] One important caveat is that the NIH National Institute on Aging (NIA) standard definition and description of AD at death is not necessarily transferrable to defining AD in life.

> **NINDS (The National Institute of Neurological Disease and Stroke) advises that AD is believed to occur in a demented patient when both abnormal amounts of amyloid beta (Aβ), accumulating extracellularly as amyloid plaques and with abnormal amounts of hyperphosphorylated tau proteins accumulating intracellularly as neurofibrillary tangles, form in the brain, affecting neuronal functioning and connectivity, resulting in a progressive loss of brain function during a person's lifetime.[7]**
>
> **The NIA further explains that in AD, as neurons are injured and die throughout the brain, connections between networks of neurons may break down and many brain regions begin to shrink. By the final stages of AD, this process—called brain atrophy—is widespread, causing significant loss of brain volume.**

On the other hand, the NIA defines dementia as:

> **The loss of cognitive functioning — thinking, remembering and reasoning — to such an extent that it interferes with a person's daily life and activities. Some people with dementia cannot control their emotions, and their personalities may change. Dementia has been defined with standard psychometric measures such as the Mini Mental Status Exam (MMSE) < 27 / 30 scale.[8]**

AD is a complex neurodegenerative, progressive dementia, with several factors at work that result in synaptic loss, neural network failure, cell death and dementia.[9] AD involves a multifactorial process that includes amyloid and tau deposition, synaptic loss, inflammation, oxidative stress and neuronal injury and loss. Soluble amyloid beta can increase synaptic dysfunction and accelerate formation of neurofibrillary tangles. Synaptic loss and neuronal death may occur as a result of many pathophysiologic events that include deficits of synaptic growth factors such as BDNF (Brain Derived Neurotrophic Factor), elevation of soluble A Beta oligomers, inflammation and oxidative stress. While amyloid plaque and tangles are pathologic hallmarks of disease at death, they are not closely correlated at autopsy with prior cognitive decline in life. Cognitive decline during life is closely correlated with the loss of synaptic connections quantified at autopsy.[10]

According to the CDC, dementia can be caused by many conditions, some of which are reversible, while others are not.[11] In addition to AD, irreversible causes of dementia include Lewy body, vascular and frontotemporal dementia. Different forms of amyloid beta have been found in people living with these non-AD dementias.[12] To further complicate the diagnostic picture, up to 83% of patients with dementia may have multiple causes of dementia occurring simultaneously with AD, commonly known as mixed dementia.[13]

People who have dementia may have a reversible underlying cause such as a side effects from medication, increased pressure in the brain, vitamin B 12 deficiency, depression, Lyme Disease and thyroid hormone imbalance, all of which can be identified and treated.

It's no wonder that clinicians are dissatisfied with the current diagnostic pathway, with many citing a high degree of subjectivity in the diagnosis and the absence of a definitive test to identify AD and distinguish it from other forms of dementia.[14]

In medical practices nationwide, primary care physicians (PCPs) as well as neurologists are following CMS current requirements to perform cognitive testing as part of the Annual Wellness Visits for Medicare recipients.[15] Cognitive Assessments and Care Plans are covered under CPT code 99483 and reimbursed when provided in an office setting.[16] PCPs will also be tasked to evaluate prescribing new treatments for AD that may slow the decline of memory and thinking, as well as function, in people living with AD.

These anti-amyloid treatments work by attaching to and removing amyloid-beta, a protein that accumulates into plaques, from the brain, although it is not certain that amyloid prevention and/or removal will prevent loss of synapses and neurons. These novel treatments will be costly, burdensome and are criticized for their marginal risk/benefit.[17] Such issues increase the need for better AD diagnostic tools in PCP and neurologist settings[18] as well as to support payer coverage decisions.

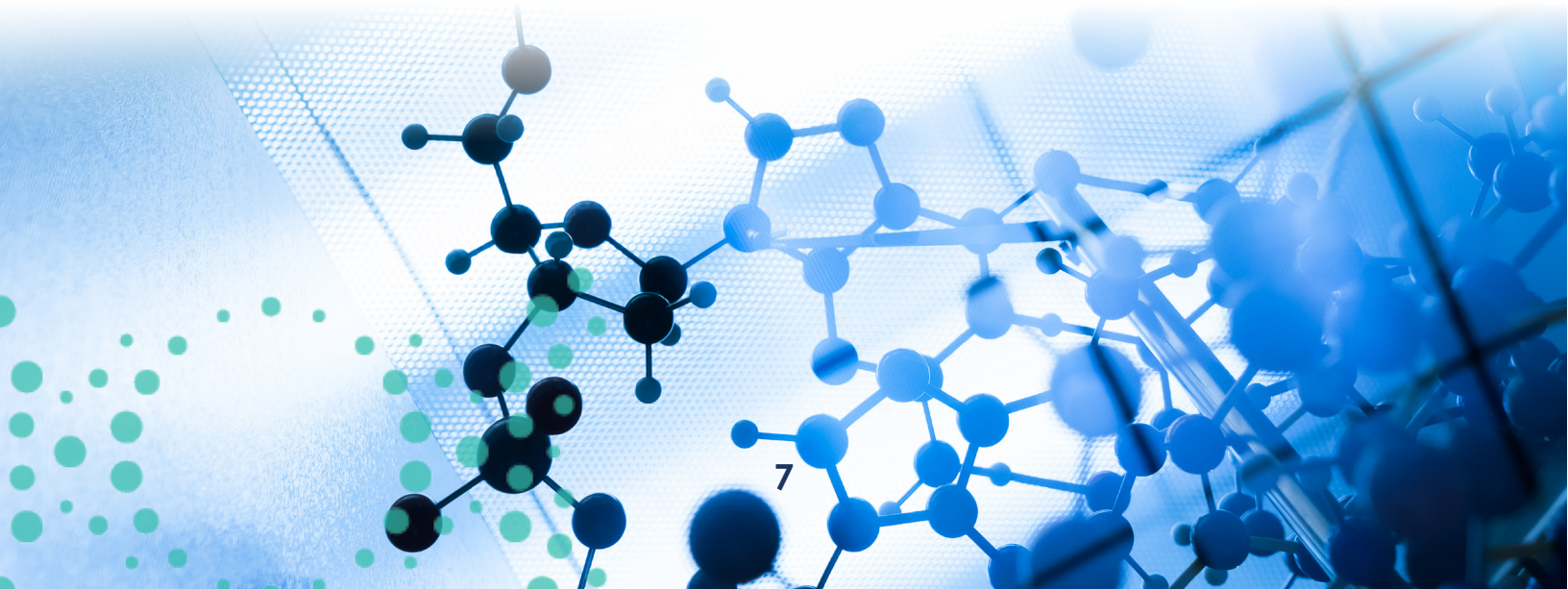
New Treatments Launched to Treat AD

- **June 2021:** FDA approved Aduhelm (aducanumab), the first amyloid beta-directed antibody for treating AD.[19] Aduhelm is a monthly infusion associated with a 24% slowing of progression of AD symptoms but is associated with Amyloid Related Imaging Abnormalities (ARIA), which affected up to 40% of patients studied.[20]

  Pharmaceutical manufacturer Biogen initially priced Aduhelm at $56,000 per year, then reduced the list price to $28,000. Due to concerns over clinical results, as well as the risk-benefit profile, CMS declined to cover Aduhelm outside of clinical trials. Furthermore, CMS stipulated that the patients can only have either (i) MCI or (ii) early AD and must have (iii) evidence of amyloid consistent with AD.[21]

- **January 2023:** FDA granted accelerated approval for LEQEMBI (lecanemab), the second amyloid beta-directed antibody indicated for the treatment of AD.[22] In clinical trials of patients with MCI due to AD or AD dementia, LEQEMBI demonstrated a 27% slowing in the rate of cognitive decline over a 12-month period.

  It is a bi-weekly, infused therapy and Eisai, the maker of LEQEMBI, has priced the therapy at $26,500 per year.[23] Due to the risk of ARIA, with signs and symptoms including headache, worsening confusion, dizziness, visual disturbances, nausea and seizures, patients will be required to have four MRI scans during the first six months of treatment to evaluate potential ARIA with edema or with hemorrhaging. CMS has not made a coverage determination yet.



New Tools Now Available: Accurately Identify AD in People Living with Dementia in the Primary Care Setting

The introduction of DISCERN™, an autopsy validated skin test developed and made available by Synaps Dx (SDx), has shown >95% sensitivity and specificity to identify AD in people recently diagnosed with dementia, even in those with mixed dementia.[24] This signals a new era for increased physician prescribing confidence and better outcomes for patients.

DISCERN is based on a 3mm skin punch biopsy that is non-invasive and can easily be administered in the generalist setting, with the skin sample then processed in the SDx CLIA approved laboratory. The test is comprised of three assays that assess the factors directly related to the formation of synaptic connections in the brain impacting loss of memory and cognition in people living with AD. The assays are also related to the formation of amyloid plaques and tau in neurofibrillary tangles, hallmarks of AD at autopsy.

The Link Between the Brain and Skin

Dementias as a whole are complex. They don't just impact thinking, memory and personality, but can also have widespread systemic manifestations, particularly early on in the disease process. For example, it has long been accepted that people with dementia due to Parkinson's disease can have systemic symptoms in the earliest or preclinical stages. Symptoms such as constipation, changes in smell and taste, erectile dysfunction and fatigue can precede the development of the motor symptoms of Parkinson's disease.[25] AD also drives systemic changes. The brain mediates and regulates every aspect of the body, including body composition. While obesity is a risk factor for the development of AD, changes in body composition such as weight loss can occur early on in the disease process. A decline in cognitive processes can cause changes to the body due to behavior or due to brain mediated functional changes. Therefore, looking at morphological changes that take place in the skin has shown to be a useful tool in the diagnosis of AD.

DISCERN has received reimbursement PLA codes (206U and 207U) and is paid for by Medicare. It is currently commercially available across the country, with the exception of New York State.

DISCERN Test Impacts Clinician Prescribing, Specialist Referrals

A clinical utility study found clinicians were 4x more likely to prescribe disease modifying therapies with a positive DISCERN test than without. These results highlight the benefit of informing a more objective and accurate diagnostic tool available in the community setting.[26]

Placing a more accurate and objective diagnostic tool in the hands of the PCP can improve the quality of referrals to neurologists for further workup.

Ruling out AD allows generalist clinicians to focus additional resources on addressing modifiable risk factors, many of which they are actively managing. The most common risk factors that can predispose people to dementia include diabetes, hypertension, cardiovascular disease and age-related musculoskeletal disorders.[27]

For delegated risk or Medicare Advantage plans, a negative DISCERN test in the primary care setting could result in significant cost avoidance from specialist referrals, invasive and expensive imaging and liquid biomarker tests (both blood and CSF), rather focusing those advanced diagnostics and targeting the new AD treatments to patients with a more definitive diagnosis of AD.

Importance of Early Intervention

As with many progressive diseases, people experiencing cognitive deficits benefit from early intervention which is recognized as key for long term success in people living with SCD or MCI. As a caveat, there is high variability in progression from MCI to dementia, with >50% of patients not progressing to dementia, let alone AD in 10 years.[28]

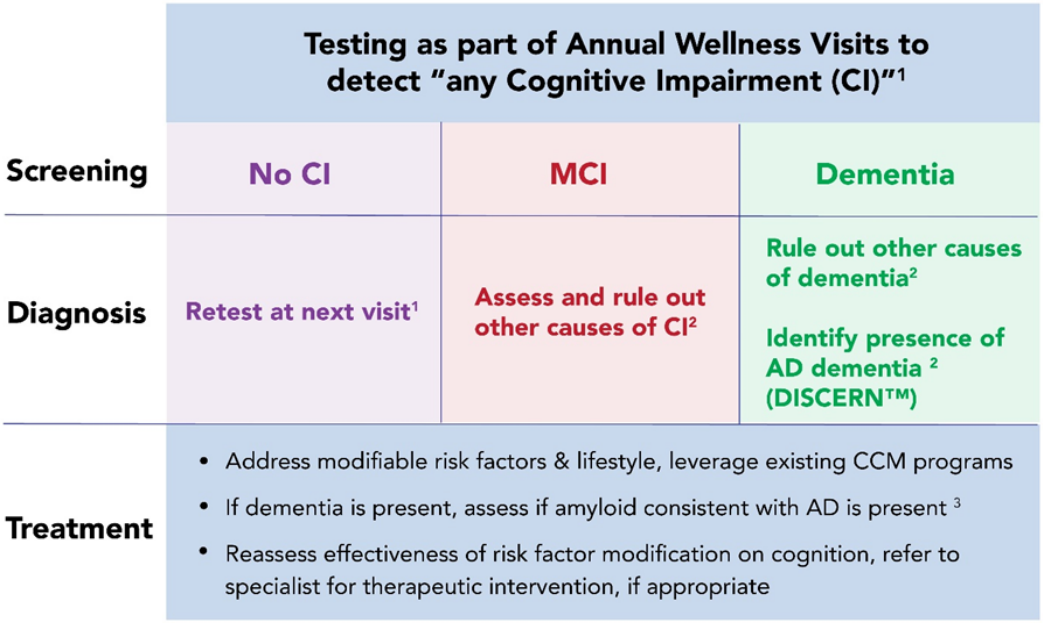
On a positive note, the CDC has identified factors such as hypertension, diabetes, depression, hearing loss, obesity, cigarette smoking and a lack of physical activities as modifiable risk factors for AD and related dementias.[29] This translates into meaningful opportunities for people to make lifestyle changes that slow disease progression.

A recent population-based study suggested that excluding genetic risk factors that are not preventable, about 40% of dementia cases in the present population could be attributable to preventable comorbid diseases, most notably diabetes, stroke, delirium and heart disease, which are also associated with increased mortality.[30]

Even modest lifestyle changes can be impactful. Data recently presented at the Clinical Trials in Alzheimer's Disease conference suggested that mild physical activity could stabilize cognition over a 12-month period in people with MCI.[31] Additionally, data was also presented that suggested that addressing modifiable risk factors through telephone counseling could also slow cognitive decline.[32]

Introducing a Potential Diagnostic Pathway

Thanks to the introduction of tools now available and recommended for the Medicare population, a potential and compelling diagnosis and treatment pathway emerges for the cost-effective management of people identified with cognitive impairment.



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This pathway paves a reliable route to provide early intervention that slows or halts cognitive decline in people with early disease. It is an economically sound approach to addressing modifiable risk factors which is now made easier with the availability of tools in the generalist setting.

- For patients with MCI, initially addressing modifiable risk factors has shown to slow or stop progression of cognitive loss in many patients before evaluating for MCI due to AD. Repeat cognitive assessments as part of the Annual Wellness Visit should be used to identify any changes in cognitive function.
- Once a patient has been identified with dementia, the DISCERN test can be initiated in the generalist setting to identify the presence of AD.
- Where AD is detected, the presence of amyloid consistent with AD can be assessed using imaging and blood biomarkers in the current diagnostic pathway, as appropriate.
- Based upon the presence of AD and amyloid, the clinician can further evaluate if the AD drugs can provide symptomatic relief, if these new drugs are appropriate for the patient or if referral to the neurologist for evaluation is indicated.
- If AD is not detected, then the clinician can look to other causes of dementia. This has the potential to reduce the burden of lumbar punctures, PET scans and other advanced imaging in the case where AD is not detected.

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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.

* 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.

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