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Neurology Solutions

Accelerating Alzheimer's Therapy Innovation: **The Power of Blood-Based Biomarkers**

Alzheimer's disease (AD) is a devastating neurological condition affecting millions of people worldwide, with the number of cases expected to rise dramatically in the coming decades. The disease progressively destroys memory, thinking skills, and the ability to carry out daily tasks, placing a tremendous burden on both patients and caregivers. Despite recent advances, challenges remain in early diagnosis and therapeutic development. Blood-based biomarker testing presents a promising solution to improve access to critical early risk assessment along with a pathway towards accelerated clinical trials for AD.

by Dr Michael K. Racke, MD, Medical Director, Neurology, Quest Diagnostics

The Global Impact **of Alzheimer's Disease**

Alzheimer's disease (AD), responsible for 60 to 80% of the 55 million dementia cases globally, presents a pressing health challenge.[1] Alarmingly, the total number of people living with dementia is expected to escalate to 140 million by 2050, emphasizing the critical need to confront this growing public health issue.[2] The impact of AD is particularly acute among older adults, with late-onset AD typically manifesting in the mid-60s and beyond. Nevertheless, it is crucial to recognize that AD is not solely confined to the elderly; a less common but equally devastating form known as early-onset AD affects individuals as young as their 30s to mid-60s.

As the foremost cause of dementia among older adults, AD exacts a profound toll on individuals, their families, and society as a whole. The relentless progression of the disease robs patients of cherished memories, cognitive abilities, and ultimately, the ability to perform even the simplest daily tasks. This emotional, psychological, and financial burden affects not only patients but also their families and caregivers.

Caregivers are often dedicated family members or close friends who provide selfless care and support. It is estimated that approximately 11 million Americans alone devote their time and effort as unpaid caregivers, contributing to the well-being of their loved ones with AD. This caregiving contribution carries a staggering annual cost of over $340 billion in the United States, highlighting both the immense dedication of these individuals and the significant societal impact of AD.[3]

The global impact of AD extends far beyond the personal struggles of those directly affected. Societies worldwide must grapple with the challenges posed by an aging population and the increasing demand for resources and healthcare services to address the rising prevalence of AD. Finding effective strategies to detect, manage, and potentially treat Alzheimer's disease is an urgent priority.

Challenges in **AD Diagnosis and Therapy Development**

The journey to diagnose and treat AD is fraught with challenges that hinder both timely diagnosis and the development of effective therapies. One of the primary challenges lies in the clinical diagnosis process, which relies on a battery of tests, including neurocognitive exams, biomarker evaluation, and brain imaging. Unfortunately, these tests are typically administered after noticeable symptoms have appeared, leading to an average delay of 2.8 years after symptom onset before patients receive a clinical diagnosis.[4] This delay allows the disease to advance significantly before intervention, potentially worsening its impact on patients' lives.

However, what exacerbates this delay is the knowledge that AD's pathophysiological changes begin silently in the brain long before any memory loss or observable symptoms emerge. This preclinical phase can extend for up to 20 years, providing a crucial window of opportunity for potential interventions.[5] Early risk identification during this phase is essential for implementing preventive measures and potentially exploring disease-modifying therapies. Unfortunately, while there are accurate biomarkers that can detect early changes, the sample/tissue type is a barrier to performing these tests routinely, which ultimately limits accessibility.

Moreover, the delayed diagnosis also impacts the design and execution of clinical trials for AD therapies. Participants recruited for clinical trials may already have experienced irreversible neurological damage by the time they are diagnosed, making it challenging to accurately assess the efficacy of potential treatments. This complication further extends trial durations and increases the overall cost and complexity of clinical research in the quest for effective therapies.

To overcome these challenges, there is a pressing need for objective biomarkers that can detect early pathological changes in the brain associated with the development of AD. Such biomarkers would facilitate early diagnosis, improve patient outcomes, and enable healthcare providers to implement personalized care plans at an earlier stage. Furthermore, reliable biomarkers can aid in identifying suitable candidates for clinical trials, allowing researchers to recruit participants during the preclinical phase, when disease-modifying treatments are most likely to be effective.

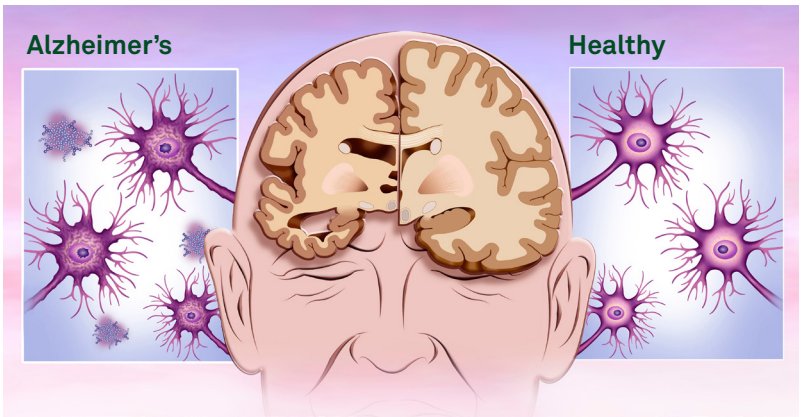
The Role of
Amyloid Proteins and p-tau in AD

To effectively combat AD, understanding its pathophysiology is paramount in developing targeted therapies and diagnostic tools. Within the intricate landscape of AD pathology, 2 key biomarkers have emerged as critical indicators: phosphorylated tau (p-tau) and amyloid proteins. These biomarkers play pivotal roles in the disease's pathophysiology and progression and have been extensively studied to gain insights into their mechanisms, enabling the development of potential therapeutic interventions.

Amyloid proteins are known for their involvement in the formation of amyloid plaques, which are abnormal protein deposits found in the brain tissue of individuals with AD. These plaques primarily consist of beta-amyloid, a peptide derived from the amyloid precursor protein. As the disease progresses, the accumulation of beta-amyloid in the brain disrupts normal cellular functions, leading to neurofibrillary tangles and neuronal damage with subsequent impairments in cognition and memory.

Concurrently, p-tau has emerged as another crucial biomarker closely associated with AD. Tau is a protein primarily expressed in neurons, where it plays a critical role in stabilizing microtubules and supporting cellular structures. In AD and other dementias, tau becomes abnormally phosphorylated, leading to its aggregation into neurofibrillary tangles within neurons. These tangles disrupt the cell's normal functions and contribute to the degeneration and eventual death of neurons, which results in the cognitive decline observed in AD patients.

The correlation between the accumulation of beta-amyloid plaques and p-tau pathology in the brain has provided essential insights into the disease's underlying mechanisms. This knowledge has fueled the development of anti-beta amyloid immunotherapies, including Biogen's Aduhelm® (aducanumab) and Biogen and Eisai's Leqembi® (lecanemab) (which received FDA approval in 2021 and July of 2023, respectively) and Eli Lilly's donanemab (which is hoped to gain FDA approval by the end of 2023), potentially slowing the disease's progression.



Source: Adobe

The UCSF Tablet-based Cognitive Assessment Tool (TabCAT)
Advancing Early Diagnosis of AD

The UCSF TabCAT Brain Health Assessment (TabCAT-BHA) is a tablet-based cognitive assessment tool developed to enhance the early diagnosis of AD and other neurocognitive disorders. Supported by Quest Diagnostics, this innovative tool is designed to be efficient and accurate, benefiting patients, families, and healthcare providers in primary care and specialty practices.

Early and accurate diagnosis of neurocognitive disorders is critical for selecting appropriate treatments, providing supportive interventions, and planning future care needs. However, cognitive impairment and dementia often remain undiagnosed, necessitating more precise assessment tools. The TabCAT BHA addresses this need by efficiently evaluating 4 key cognitive domains typically affected in neurocognitive disorders: **memory, executive function and speed, visuospatial skills, and language.**

One of the unique features of the TabCAT BHA is its informant survey, which enables evaluation of functional decline and neurobehavioral changes. This survey aids in the detection of atypical presentations of AD and other non-AD disorders, increasing the diagnostic accuracy in primary care settings. With a 10-minute administration time and automated scoring, the TabCAT BHA can be seamlessly integrated into busy clinical practices.

The TabCAT BHA is an example of a digital diagnostic that demonstrates high sensitivity and specificity in detecting mild cognitive impairment (MCI) and dementia. This partnership showcases Quest's commitment to enhancing the overall ability to accurately diagnose AD and other neurocognitive disorders at the earliest possible stage. By supporting the development of cutting-edge assessment tools like the TabCAT BHA, Quest Diagnostics is playing a crucial role in advancing early diagnosis and improving patient outcomes in the fight against neurocognitive disorders.

To learn more, visit
https://memory.ucsf.edu/research-trials/professional/tabcat

ALZ Match: Enabling Patient Identification and Trial Matching for Alzheimer's Research

Quest Diagnostics is committed to advancing AD research and supporting pharmaceutical companies in their pursuit of effective treatments. Through ALZ Match, Quest is playing a crucial role in **identifying individuals at increased risk of developing Alzheimer's, thereby facilitating better-targeted clinical trials programs.**

ALZ Match is a unique registry of patients who have undergone the Quest AD-Detect™ Amyloid Beta 42/40 Ratio test or other risk assessment tools and have opted-in to be notified if they are eligible for screening in research studies. This proactive approach not only provides individuals with vital insights into their Alzheimer's risk but also offers pharmaceutical companies a valuable resource to identify suitable candidates for clinical trials.

By offering a simple blood test conducted at Quest Diagnostics laboratories, ALZ Match enables individuals to determine their eligibility for research studies focused on AD. The study is actively recruiting participants by invitation only, ensuring a targeted and well-defined pool of individuals for potential trial matching.

For pharmaceutical companies seeking to develop treatments for AD, ALZ Match presents an unparalleled opportunity to connect with pre-screened individuals at higher risk for the disease. This novel registry aids in streamlining the recruitment process, reducing time and resources, and ultimately facilitating more efficient clinical trials.

Quest Diagnostics is proud to lead the charge in the fight against AD through ALZ Match. By working hand-in-hand with pharmaceutical companies, Quest aims to accelerate the development of effective therapies and improve the lives of those affected by this devastating condition.

For more information about ALZ Match and how pharmaceutical companies can collaborate in this groundbreaking effort, please contact Quest Diagnostics at Pharma.QuestDiagnostics.com. Together, we can make a significant impact on AD research and move closer to a future free of this challenging disease.

Blood-Based Biomarker **Risk Assessment**

Quest Diagnostics, the largest independent diagnostic lab in the United States, has been at the forefront of developing innovative tools for AD diagnosis. Nearly two decades ago, the company's Athena Diagnostics division introduced a groundbreaking test to detect AD biomarkers using cerebrospinal fluid (CSF). This CSF test was a significant advancement at the time, offering valuable insights into AD pathology, and has served as a critical diagnostic tool since.

Building upon this heritage, Quest continues to drive progress in the AD diagnostic landscape. Recently, the company unveiled an innovative blood-based biomarker test called AD-Detect™ Amyloid Beta 42/40 Ratio. This test measures beta-amyloid biomarkers in the blood, providing a non-invasive and accessible alternative to CSF testing. By analyzing the beta-amyloid 42/40 ratio, AD-Detect can accurately assess pathophysiological markers associated with amyloid deposition and cognitive decline. Lower ratio values indicate a higher risk, enabling early identification and potentially opening doors to new therapeutic strategies.

The versatility of AD-Detect serves several important purposes in the fight against AD. First, it allows for the establishment of a baseline risk assessment for individuals. Detecting and monitoring changes in beta-amyloid levels over time are critical in understanding disease progression and guiding personalized treatment plans. Second, with its high sensitivity and specificity, AD-Detect has the potential to identify individuals at risk of AD years before observable symptoms appear. This early detection paves the way for timely interventions or other preventive measures to potentially delay or mitigate disease progression.

For drug developers and researchers in the field of AD therapeutics, AD-Detect offers significant advantages in clinical trial recruitment and design. By identifying potential clinical trial participants before significant disease progression occurs, pharmaceutical sponsors can more accurately assess therapy efficacy, and participants can benefit from therapies when disease-modifying interventions are most likely to be effective.

Benefits of **Blood versus Imaging** (MRI, CT, and PET) and CSF

While imaging, including MRI, CT and PET scans, and CSF tests have been valuable in the diagnosis and monitoring of AD, blood-based biomarker testing offers several distinct advantages that make it a more accessible and efficient option for patients and healthcare providers:

Non-Invasive and Painless Procedure

A significant advantage of blood-based biomarker testing is its non-invasive nature. Collecting a blood sample is a routine procedure, requiring only a needle stick, making it relatively painless and easily acceptable for patients of all ages. In contrast, PET scans involve the injection of a radioactive tracer, and CSF tests require a lumbar puncture, both of which are more invasive and may cause discomfort and anxiety for patients. The ease and simplicity of blood-based testing increase patient compliance and allow for frequent monitoring, critical in understanding disease progression.

Accessibility and Convenience

Blood-based biomarker tests offer unparalleled accessibility and convenience, enabling a broader population to access early diagnosis and monitoring for AD. Compared to PET scans, which are costly and often limited to specialized medical centers, blood tests can be performed in a wide range of healthcare facilities, including local clinics and primary care offices, or any of Quest's 2,100 patient service centers (PSCs) located throughout the United States. This accessibility reduces the need for patients to travel long distances and streamlines the diagnostic process, ensuring that more individuals can benefit from early detection and intervention.

Early Detection and Intervention

One of the most significant advantages of blood-based biomarker testing is the potential for early detection of AD, even before noticeable symptoms appear. As the disease process begins years before clinical symptoms manifest, early detection is crucial for implementing preventive measures and potential therapeutic interventions. Blood tests like AD-Detect Amyloid Beta 42/40 Ratio have the capability to identify individuals at risk for AD long before cognitive impairment becomes evident-and often long before plaque build-up becomes visible in imaging. This early knowledge empowers healthcare providers to proactively address lifestyle factors and potentially explore emerging therapeutic options.

Longitudinal Monitoring and Disease Progression

Blood-based biomarker tests, like AD-Detect, offer the advantage of longitudinal monitoring of disease progression. Regular follow-up blood tests can track changes in beta-amyloid biomarkers, providing insights into disease advancement and therapeutic responses. This continuous monitoring can be especially useful in clinical trial settings, where the efficacy of potential treatments can be assessed over time. In contrast, PET scans and CSF tests may be less suitable for frequent monitoring due to their cost and invasiveness.

Cost-Effectiveness

Blood-based biomarker tests are generally more cost-effective compared to imaging and CSF tests. The reduced cost and accessibility of blood tests make them more attractive for large-scale population screening and clinical trial recruitment. Cost-effectiveness plays a crucial role in promoting the widespread adoption of biomarker testing and facilitating its integration into routine healthcare practices.

Quest Diagnostic Leadership in **Neurological Diagnostic Testing**

Quest Diagnostics commitment to establishing Advanced Neurology as a leading center of excellence in the industry is evident in its comprehensive neurology testing menu. With more than 400 neurology tests powered by 15 distinct methodologies, the company provides a wide array of diagnostic tools for various neurological conditions, including AD and other types of dementia. Quest's AD/Dementia portfolio includes:

AD-Detect™ Amyloid Beta 42/40 Ratio

This blood-based (plasma) test assesses one of the earliest biomarkers of AD[6] and is shown to be as effective as CSF testing and amyloid PET scans.[7]

AD-Detect™ Apolipoprotein E (ApoE) Isoform

This blood-based (plasma) test detects isoforms of ApoE, which is a key genetic biomarker and strong genetic risk factor for AD.[8]

Dementia Panel, RestoreU™

This blood-based panel leverages Quest Advanced laboratory services and AI-based technology from uMETHOD Health to deliver personalized treatment recommendations that address key contributors to memory loss, dementia, and mild cognitive impairment.

Beta-Amyloid 42/40 Ratio and Apolipoprotein E (ApoE) Isoform Panel

This CSF panel combines results for Aβ42/40 ratio and ApoE into an algorithm to assess the cause of mild cognitive impairment and the risk of AD.

Apolipoprotein E (ApoE) Isoform

This is a CSF test used to detect ApoE, a key biomarker for AD. Patients with ApoE4 (which directly influences amyloid-beta and tau pathology as well as neuroinflammation) have an increased risk of developing AD.[8]

ADmark® Phospho-Tau/Total Tau/Aβ42 Analysis and Interpretation (CSF)

The combination of the 3 biomarkers phospho-tau, total tau, and Aβ42 enables a more accurate diagnosis of AD. CSF tau/Aβ42 ratio may be predictive of future dementia in cognitively normal adults.[9]

About the **Author**

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Dr Michael K. Racke is the Medical Director for Neurology at Quest Diagnostics. He is a leader in the field of neurology and neuroimmunology with special expertise in multiple sclerosis.

Dr Racke's research focuses on developing novel tests for neurologic disorders, including monitoring therapeutic responses in diseases such as multiple sclerosis. He has authored more than 200 peer-reviewed papers, book chapters, and reviews on the pathogenesis of neuroimmunology diseases. He has over 3 decades of leadership experience in academia and clinical practice and continues to serve on several national professional society committees.

Dr. Racke is board-certified by the American Board of Psychiatry and Neurology and is a member of the American Academy of Neurology and American Association of Immunologists.

Why Apolipoprotein E (ApoE) **testing matters**

ApoE and AD Risk:

Gene Variants
There are 3 major alleles (variants) of the *ApoE* gene: ε2, ε3, and ε4. These alleles lead to different forms of the ApoE protein.

Risk Association
The ApoE ε4 allele is associated with a higher risk of developing AD. Individuals carrying one ε4 allele have an increased risk, and those carrying two ε4 alleles (homozygous) have an even higher risk. Conversely, the e2 allele might confer some protection against AD.

Amyloid Beta Accumulation
One theory suggests that ApoE ε4 promotes the accumulation of amyloid-beta plaques in the brain, a hallmark of AD. ApoE ε4 might influence both the deposition and clearance of amyloid-beta.

ApoE and ARIA in Anti-Amyloid Immunotherapy:

What is ARIA?
Amyloid-Related Imaging Abnormalities (ARIA) refers to findings on MRI scans that can occur in some people receiving anti-amyloid immunotherapies for AD. ARIA can manifest mainly as two types: ARIA-H (indicative of microhemorrhages or hemosiderin deposits) and ARIA-E (representing vasogenic edema).

ApoE ε4 and ARIA
Clinical studies have indicated that individuals with one or more ApoE ε4 alleles have a higher risk of developing ARIA when treated with certain anti-amyloid immunotherapies.

Implication for Treatment
Given the increased risk of ARIA in ApoE ε4 carriers, patients undergoing anti-amyloid immunotherapy might be tested for their ApoE genotype. Knowing a patient's ApoE status can help in risk stratification, informed decision-making about therapy, and monitoring during treatment.

Beyond its diagnostic offerings, Quest Diagnostics actively contributes to advancing science in the field of dementia through academic research and collaborations. The company is **excited to work with pharmaceutical companies and research partners on its QuestForTheCure,** aiming to further innovation and drive progress in AD and dementia research.

Conclusion

Blood-based biomarker testing, exemplified by Quest Diagnostic AD-Detect Amyloid Beta 42/40 Ratio, holds immense potential to improve access to early diagnosis of AD and revolutionize therapy development and clinical trials. By enabling early intervention and more accurate efficacy assessments, this innovative approach can help alleviate the burden of AD on patients, caregivers, and society. Quest Diagnostics commitment to advancing neurological diagnostic testing and contributing to dementia research further reinforces the hope of transforming the landscape of AD and other neurological conditions.

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