

BLOOD-BASED BIOMARKERS: UNBURDENING THE NEURODEGENERATIVE DISEASE DIAGNOSTIC JOURNEY

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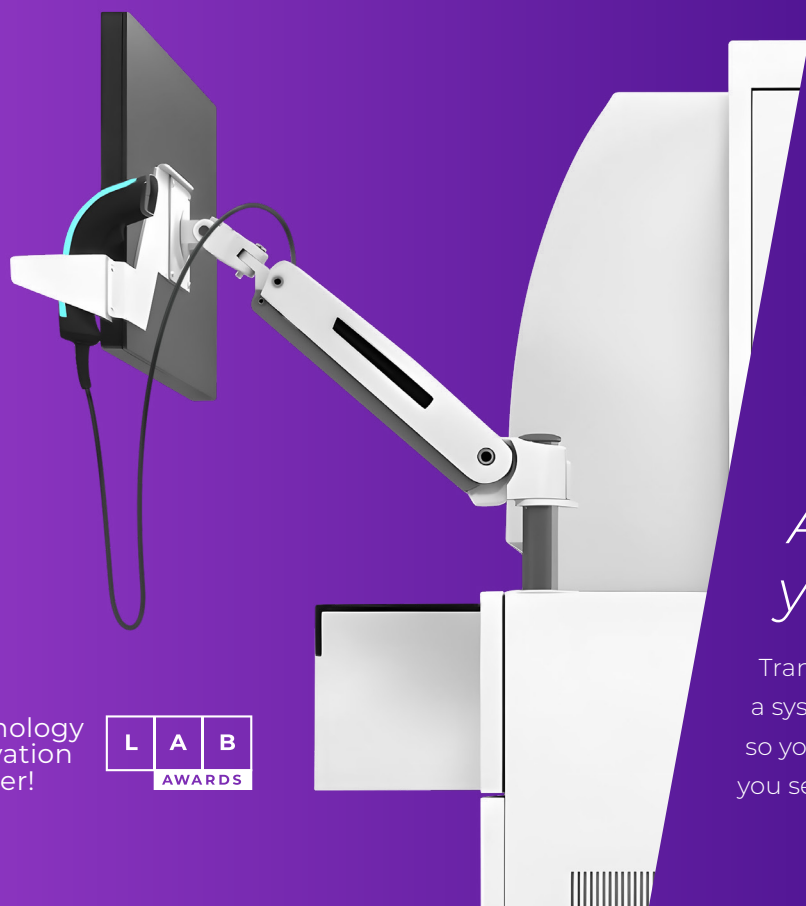
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TRACKING THE IMPACT OF BLOOD-BASED BIOMARKER ASSAYS

Highly sensitive assays are changing the landscape of Alzheimer's disease diagnostics and pharmaceutical clinical trials.

Early and accurate diagnosis of neurodegenerative disease, particularly Alzheimer's disease, can significantly impact treatment, disease progression, and patient outcomes. In an interview with *The Scientist*, Lawrence Honig, a professor of neurology at Columbia University's Irving Medical Center, discussed the importance of highly sensitive assays in Alzheimer's disease diagnostics and drug development.



Lawrence Honig, a professor of neurology at Columbia University's Irving Medical Center and director of the NYS Center of Excellence for Alzheimer's Disease, is blazing the trail to better diagnosis and treatment of Alzheimer's disease.

LAWRENCE HONIG

What is the current state of early Alzheimer's disease diagnosis?

Regretfully, in the United States and worldwide dementia is often only recognized in the very late stages. Even in countries with high GDP, socioeconomic status, and medical care, many dementia patients are first diagnosed at a relatively advanced stage of moderate or severe dementia. The standard journey of someone who presents with a cognitive or memory concern is to perform a thorough neurological examination, including mental status testing. We perform certain basic laboratory tests to establish general medical status as well as brain imaging and spinal fluid biomarker testing.

How are imaging and cerebrospinal fluid biomarker testing used for diagnosis?

The label for disease-modifying drugs states that we should not treat people with anti-amyloid antibodies without amyloid confirmation. There are two main methods for confirming amyloid: PET scanning and cerebrospinal fluid biomarker testing. PET scanning can help establish whether there is amyloid deposition in the brain with a good degree of sensitivity and specificity, but only looks at β amyloid. Spinal fluid testing allows us to look at various proteins, including β amyloid and various phosphorylated tau proteins. Spinal fluid biomarkers and amyloid PET scans revolutionized the field, but they have a heavy resource burden. Also, like any test,

they can be indeterminate. For example, in some cases, people can be PET negative but CSF positive. Discrepancies between the various CSF biomarkers complicate diagnosis and treatment.

How can blood-based biomarkers aid Alzheimer's disease diagnosis?

Blood-based biomarkers are key for achieving accurate early diagnosis, making informed treatment decisions, and giving people prognostic information. Recently, the FDA approved the first laboratory blood test for Alzheimer's disease diagnosis in clinically symptomatic people. The test has been approved based on its comparable performance to a cerebrospinal fluid test. It had 92 percent positive predictive value based on what has been reported so far.

How do the latest analytical tools help improve blood-based biomarker development?

The blood-based biomarker revolution includes better antibodies, assays, and instrumentation. Highly sensitive and specific analytical platforms are import-

ant for blood-based analysis. Sensitivity is particularly important because these analytes are present at much lower concentrations in blood. Cerebrospinal fluid bathes the brain, so the brain analytes are often present in quite reasonable concentrations. Blood-based assays must be reproducible and accurate for relatively low concentrations of analytes. The latest platform advancements address this and are based on tuning immunoassays to be extremely sensitive without sacrificing specificity.

How do blood-based biomarkers help Alzheimer's drug development?

Biomarker confirmation of Alzheimer's disease for clinical trial participants is crucial because if a significant fraction of a trial population does not have the disease you are trying to treat, the power for detecting an effect of the drug is much lower. Phosphorylated tau levels in blood can indicate whether the individual is likely to have Alzheimer's disease, allowing us to determine good clinical trial candidates using a quick blood test. By not subjecting ineligible candidates to unnecessary radiation, lumbar punctures, or other tests before establishing whether there is a reasonable likelihood that they have Alzheimer's disease, we can reduce the burden to participants, clinical investigators, and resources. That is a tremendous advantage.

This interview has been condensed and edited for clarity.

Dr. Honig reports consulting for Beckman Coulter, BioArctic, Biogen, Eisai, Genentech, Lilly, Medscape, New Amsterdam, Prevail, and Roche, and receiving institutional research support from NIH/NINDS, NIH/NIA, New York State Dept of Health, Lewy Body Disease Association, CurePSP, Abbvie, Acumen, Alcotar, Alnylam, Biogen, Bristol-Myer Squibb, Cognition, EIP, Eisai, Ferrer, Genentech/Roche, Janssen/Johnson and Johnson, Transposon Therapeutics, UCB, and Vaccinex.



ADDRESSING THE DIAGNOSTIC HEALTHCARE BURDEN OF NEURODEGENERATIVE DISEASES

The global healthcare burden for diagnosing neurological diseases such as Alzheimer's disease (AD) is tremendous. Rapid and efficient detection of neurodegenerative diseases and their subsequent treatment and monitoring are important factors for optimizing patient outcomes. However, current gold standard diagnostics such as positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) testing are expensive and have long wait times given that they are performed in major medical centers and by specialized health providers already facing healthcare system burdens.¹ In the case of CSF testing in particular, the invasiveness and perceived risk and pain of the procedure by patients may further complicate the testing process.

Many patients face significant obstacles navigating the diagnostic landscape due to the burden of long wait times and high costs, which is particularly impactful for those who are socioeconomically underprivileged. This disparity creates an additional burden for already stretched healthcare systems, particularly for specialized centers that are struggling to keep up with care for the rising numbers of patients with AD.

Alleviating Diagnostic Bottlenecks

Given the adverse effects that diagnostic bottlenecks have on delaying AD diagnosis and subsequent treatment and monitoring, alternative testing options that are more scalable and accessible are needed. Those that require less specialized admin-

The right diagnostic tools that are less invasive and easier to administer and interpret can provide primary care physicians with the power to perform routine screening for neurodegenerative diseases such as AD, thereby offsetting the diagnostic burden on healthcare systems.

istration are particularly promising for alleviating the global healthcare system diagnostic burden because they enable primary care providers to take a more active role in early screening and diagnosis.²

Primary care providers tasked with assessing their patients' cognitive impairments currently rely on a referral approach to specialized centers for PET and CSF evaluation. The right diagnostic tools that are less invasive and easier to administer and interpret can provide primary care physicians with the power to perform routine screening for neurodegenerative diseases such as AD, thereby offsetting the diagnostic burden on healthcare systems.

Eliminating long wait times enables early detection and subsequent initiation of treatment during the prodromal stages of disease when therapeutic efficacy and patient outcomes are maximized.¹

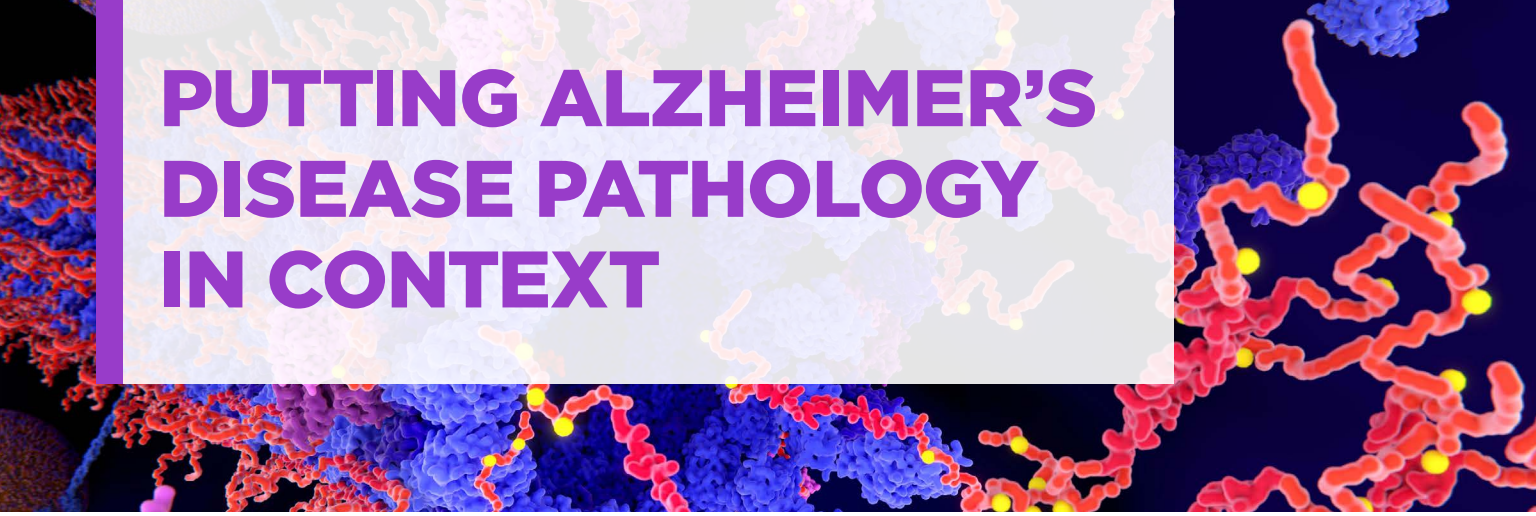
The Promise of Blood-Based Biomarker Diagnostics

Blood-based biomarkers have the potential to alleviate the burden of AD diagnosis on global healthcare systems.² There are many promising candidates for AD blood-based bio-

marker panels that may reduce the reliance on these other procedures by targeting the various biomarkers that are released into the bloodstream and act as quantifiable signals of disease presence or progression. However, additional research is needed to validate their accuracy and demonstrate that they closely represent and align with gold standard CSF and PET testing.

Among the main goals for advancing AD blood-based biomarker diagnostics is to standardize the tests so that they have a high degree of sensitivity and specificity across broadly varying patient populations and clinical settings.³ By advancing their generalizability and reliability, researchers developing such assays work towards the widespread clinical translation of these tools in primary care settings. Such a simple, non-invasive blood biomarker screening test may identify prodromal cases of AD quickly and efficiently, bypassing the need for PET and CSF testing for initial disease detection. In doing so, the benefits of novel emerging treatments can be maximized by initiating therapy early in the course of the disease.

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PUTTING ALZHEIMER'S DISEASE PATHOLOGY IN CONTEXT

The pathological changes that occur in neurological disorders such as Alzheimer's disease (AD) can be identified and tracked by measuring alterations in the levels of specific central nervous system (CNS) biomarkers throughout the course of the disease. Among these are β -amyloid, which can be found in the cerebrospinal fluid (CSF) during the prodromal phase of AD, and phosphorylated tau 217 (p-Tau217) or -181, which increase as the disease progresses. Along with measurements of these biomarkers in CSF samples, positron emission tomography (PET) brain imaging provides physicians with a visual representation of the protein plaques and tangles that deposit themselves in the brains of patients affected by AD.

These gold standard approaches assess AD biomarkers in the CNS. Because these biomarkers also make their way into the general circulation after traversing the blood-brain barrier, they can also be measured in peripheral blood samples. Since their concentration is lower there, blood-based AD biomarker assays must be highly sensitive and specific to be clinically comparable to current best practice CSF biomarker testing.¹ Another promising early screening tool is apolipoprotein E (APOE) $\epsilon 4$ testing, based on the heightened genetic risk of AD related to the presence of the $\epsilon 4$ allele of APOE.

Accommodating the Evolving Landscape of AD Research

As scientists gain a deeper understanding of AD pathology and advance the discov-

Developing novel blood-based biomarker diagnostics that accommodate the rapidly evolving AD research landscape requires a versatile, flexible, and scalable platform.

ery and development of novel therapies, the need for flexibility in accommodating scientific shifts grows. For example, the longstanding focus on β -amyloid as the go-to biomarker for early AD diagnosis is yielding to a growing understanding of the diagnostic potential of p-Tau, based on novel scientific insights into its role in disease pathology and progression.² p-Tau217 in particular is elevated in the presence of amyloid pathology and can be identified in blood samples at early and later AD stages, providing insight about disease trajectory. p-Tau217's utility as a biomarker extends to its ability to distinguish AD from other neurodegenerative diseases based on the specific correlation of this p-Tau variant with the neurofibrillary tangles unique to AD.

Developing novel blood-based biomarker diagnostics that accommodate the rapidly evolving AD research landscape requires versatile, flexible, and scalable platforms. Novel research use only (RUO) assays that can rapidly incorporate new research findings into their development enable further scientific discovery of disease mechanisms, in an ever-advancing loop of innovation and progress.

Transforming Blood-Based Biomarker Assay Development

Beckman Coulter's globally available Dxl 9000 Immunoassay Analyzer is a sensitive and flexible platform that supports

blood-based neurological biomarker development. With broad-based testing capacity for high-throughput workflows, the technology helps researchers develop and refine blood-based biomarker assays. By prioritizing sensitivity, precision, and scalability, the fully automated device helps researchers overcome workflow bottlenecks and associated challenges related to reproducibility and accuracy, without compromising analytical performance.

Recognizing the critical need to capture low levels of AD-associated protein biomarkers in blood samples for fundamental research, including the exploration of disease mechanisms, identification of potential research markers, and evaluation of therapeutic candidates, the Dxl 9000 Immunoassay Analyzer is poised to advance high-sensitivity neurological blood-based assays. The ability to easily integrate promising antibodies, such as p-Tau217,² into the platform is opening new avenues for assay development and providing researchers with a powerful tool to standardize high throughput broad-based testing and further inform scientific progress with a focus on future clinical translation. This is particularly powerful when combined with emerging drug treatments that have the most impact during early stages of the disease.

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Integrating Blood-Based Biomarkers into the AD Diagnostic Journey

Early screening and diagnosis of Alzheimer's disease (AD) is needed for initiating timely treatment, mitigating disease progression, and improving patient outcomes.¹ As scientists make gains in advancing biomarker-guided targeted therapies, many of which have peak effectiveness during prodromal stages of AD, the need for early diagnosis is even more pressing. Gold standard tests such as positron emission tomography (PET) brain imaging and cerebrospinal fluid (CSF) assay of disease biomarkers are limited by long wait times, prohibitive costs, and perceived invasiveness, contributing to a global diagnostic burden on healthcare systems. Highly sensitive blood-based biomarker assays that have the potential to be used by primary care physicians in the future during early patient screening, may address diagnostic delays, ease healthcare system burdens, and improve patient outcomes through early diagnosis and treatment.²⁻⁴

Primary Care Physician

Blood-based biomarker assays have the potential to enable early diagnosis of individuals at high risk of developing AD. There is future potential for primary care physicians to incorporate non-invasive, rapid blood testing into early screening protocols, along with clinical assessment and cognitive testing. Current guidelines do not indicate this yet, but the potential exists for alleviating the diagnostic burden on global healthcare systems.



Triaging

Patients can be triaged at specialized centers for additional confirmatory imaging and testing as needed to help inform treatment plans. However, sensitive, specific, rapid, and cost-effective blood-based biomarker assays may eventually replace PET imaging and CSF tests.⁵



Treatment Planning

New AD therapies are emerging at a rapid pace. Blood-based biomarker assays have the potential to enable rapid AD diagnosis and confirm pathology for faster, more accurate treatment planning.⁵ This is particularly important for therapies that are maximally effective when administered early in the disease course.



Treatment Monitoring

Primary care physicians have the potential to administer subsequent blood-based biomarker assays during AD treatment and clinical follow-up. This holds promise to streamline patient monitoring and enable flexible and rapid adjustments to therapies based on patient status at any given time, further offsetting the burden from global healthcare systems.



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Article 2: Addressing the Diagnostic Healthcare Burden of Neurodegenerative Diseases

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Article 3: Putting Alzheimer's Disease Pathology in Context

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