Benefits and Risks of New Tests for Alzheimer's Disease

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Alzheimer disease (AD) is the most common form of dementia with a prevalence of approximately 10% in people aged 65 years and older.[1] Current methods used to aid in the diagnosis of AD, such as cerebrospinal fluid (CSF) analysis or positron emission tomography (PET) scanning of specific AD biomarkers, have been instrumental in reducing misdiagnosis and guiding management of patients with mild cognitive impairment (MCI).[2–4] However, these methods can be costly, burdensome, and often unavailable to patients seeking a diagnosis.[5,6] A newer diagnostic approach requiring a simple blood test has been developed that may help address these barriers.[7] Notwithstanding initial excitement among providers, this recent development also raises several important public health questions: Who should receive testing? What is the psychological impact of a positive test? How will results guide treatment? and many other concerns and implications.

New blood-based biomarkers for diagnosing AD represent a significant advance in early and accessible detection of the disease. These tests measure various isoforms of amyloid-β and phosphorylated tau, correlating these values to risk of AD with accuracy that approximates current diagnostic methods. For example, a recent study showed that percent phosphorylated tau 217 (p-tau217) plasma levels and amyloid-β 42: amyloid-β 40 (Aβ42:Aβ40) ratio each have a diagnostic accuracy of 90% for AD, comparable to CSF analysis and PET scan.[8] Yet, unlike CSF analysis and PET scans, blood testing is minimally invasive and less expensive. It is also more accessible to patients residing in rural or resource-limited settings where traditional AD testing can be scarce. The simplicity and convenience of blood-based biomarkers hold potential to facilitate broader screening efforts, enabling earlier diagnosis and intervention that can more favorably alter the trajectory of an otherwise devastating condition that severely taxes caregivers and society. Although current guidelines do not yet include the use of blood-based biomarkers for AD diagnosis, without confirmatory data from PET scans and CSF analysis, they are being considered as a potential screening tool for individuals with cognitive impairment.[7,9,10]

Moreover, AD blood-based biomarkers may hold promise as surrogate markers. As opposed to biomarkers that only act as indicators for biological processes of diseases, surrogate markers act as substitutes for clinical end points, often predicting disease progression and even treatment response.[11] Some examples of surrogate markers include hemoglobin A1c for diabetes mellitus, blood pressure for hypertension, and estimated glomerular filtration rate for chronic kidney disease.[12] Changes in these markers are directly correlated with disease outcomes. Likewise, preliminary evidence suggests that AD blood-based biomarkers correlate with clinical response to pharmacologic AD treatment in terms of delaying AD progression.[13] Targeted medication management of common comorbidities, such as metformin for diabetes,[14] glucagon-like peptide 1 agonists for obesity,[15] and selective serotonin reuptake inhibitors for major depressive disorder,[16] have all correlated with improved cognition in early AD, including corresponding AD biomarker responses. Moreover, adoption of certain lifestyle changes including diet, exercise, stress management, group support, and nutritional supplementation can enhance cognition in early AD, along with improvement in AD blood-based biomarkers.[17]

A blood-based biomarker for AD may also influence psychological well-being and health-related behaviors by providing a measurable metric in a convenient and accessible manner. Studies in other fields of medicine suggest that serial biomarker testing can motivate healthy lifestyle changes and treatment adherence. Research on cardiovascular biomarkers has shown that patients who learn they are at high risk for heart disease are more likely to adopt healthier behaviors, such as improving diet and exercise routines when they can connect their treatment to an improved metric.[18]

Testing for amyloid is becoming more popular with the recent FDA approval of anti-amyloid treatments because the presence of brain amyloid is required to receive these drugs for the treatment of mild AD and MCI. People with very minimal cognitive impairment are getting tested, and the interpretation of the test results is

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sometimes misunderstood. Although the brain abnormalities that these tests reveal develop gradually over decades, doctors, patients, and family members may interpret the test results as positive or negative without considering the nuances of a gradually progressive buildup of brain amyloid that does not precisely track the emergence of clinical symptoms.

The presence of brain amyloid alone is insufficient to confirm rapid disease progression since tau accumulation correlates better with disease progression than does amyloid. A recent study of older adults without cognitive impairment showed that 0.5% of participants who were negative for both amyloid and tau progressed to dementia after 3 years, while 1.0% of those who were amyloid-positive and tau-negative and 20% of those who were positive for amyloid and had extensive tau levels developed dementia during that same time period.[19] Some people who receive a positive amyloid test result may be convinced that they are rapidly developing dementia but may never experience it in their lifetime. This nuanced impact of testing for AD is reflected in a 2020 study showing that individuals receiving biomarker results experienced increased anxiety when they perceived the information as a definitive prediction of a more fatalistic, deterministic disease outcome.[20]

In the near future, however, evidence from AD diagnostic studies could support a paradigm shift whereby individuals informed of elevated amyloid or tau plasma biomarkers are more likely to engage in cognitive training, physical activity, and other lifestyle modifications aimed at preserving brain health when they can observe their numbers stabilizing or even improving over time. Presently, while these tests hold tremendous potential to empower patients, their psychological effects underscore the need for careful communication and support during the diagnostic process. By bridging the gap between pathology detection and actionable health behaviors, surrogate markers can one day inspire patients to manage their AD risk proactively and with a renewed sense of hope.

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