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Editorial

The Future is Now: Advancing Blood-Based Markers

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Alzheimer's disease (AD) blood biomarkers (BBMs) may revolutionize the diagnosis of AD in the future. Although they are not yet ready for widespread use (1), BBMs are important and valuable for current research trials and cautious initial use in specialized memory clinics. However, additional data in larger and diverse populations are required before BBMs can be used as stand-alone tests for diagnosis by clinicians without the specific training around these tools.

In the paper by Angioni et al, the authors note that, "There is very little prospective data available where plasma samples were obtained longitudinally over a long period of time and AUCs calculated from a predetermined cut point. Such data should be required before implementation into clinical practice." (2). This is further emphasized and supported in the recently published appropriate use recommendations (AUR) by Hansson et al, including an expert workgroup of international clinicians and researchers (1). The Alzheimer's Association convened this expert group to develop the AUR for BBMs. Today, BBMs for AD are actively and rigorously being incorporated into clinical trials' design as well as contributing to the interpretation of results around target engagement. However, the implementation of such markers in trials and practice must be done in a careful and controlled way so as not to accidentally cause more harm than good. Much more research is needed before widespread clinical use of BBMs in everyday practice.

Numerous clinical studies are incorporating BBMs related to AD measures as part of the trial recruitment and enrollment funnel with the goal of improving and streamlining the process. Hansson et al "recommend use of BBMs as (pre-)screeners to identify individuals likely to have AD pathological changes for inclusion in trials evaluating disease-modifying therapies, provided Alzheimer's status is confirmed with positron emission tomography (PET) or cerebrospinal fluid (CSF) testing." (1) For instance, BBMs may be used as part of clinical trials for exploratory outcomes or to identify individuals who likely have AD-related brain changes as exclusionary for studies. Angioni et al reference the recent data from the AHEAD 3-45 study that suggests a benefit of predictive value from 28.9% of PET eligible participants to 61.5% by using BBMs as a pre-screening method (2-4). The TRAILBLAZER-ALZ 3 is utilizing BBMs in a preclinical population for inclusion without confirmation of the measures through amyloid with PET or CSF in all participants (2, 5). Studies like AHEAD 3-45 and TRAILBLAZER-ALZ 3 also present opportunities to prospectively collect blood and plasma samples for future study and investigation. The Alzheimer's Association recently provided the study team additional funding to store and actively share blood/plasma samples collected through the AHEAD 3-45 study.

In addition, rigorous data sources will be created from inclusion of these tools in clinical trials, allowing for stratification of the patient population as part of enrollment, and creating a more thorough understanding of patient response within and across trials. BBMs have the potential to produce a deep well of information to better understand potential treatment effects within and across drug classes or different mechanisms of action that support a more personalized approach to AD therapeutics in future clinical practice.

While multiple groups are making great progress in assay platform development in terms of robustness and regulation, there is still a need to focus on prospective data collection to support accuracy. As Angioni et al note, accuracy is "clinical performance [that] is demonstrated in the population in which the test will be used in clinical practice." (2) In particular, Angioni et al comment that, "If it is assumed that BBM[s] are demonstrated to be stable and robust in a prospective setting, BBM [s] could be used in primary care." (2) Indeed, Hansson et al and Angioni et al agree that there is still great concern that the effects of variables such as underlying health conditions, comorbidities, sex, race, and ethnicity have not yet been thoroughly examined in retrospective or prospective studies to determine their impact on the Accuracy of the results in broader clinical practice (1, 2). In addition, not mentioned by Angioni et al, are the potential confounding effects of common medications on one or more of the AD BBMs.

Inconsistent performance could result in disproportionate misdiagnosis or unreliable results across individuals. Hansson et al recommend specific guidance for current use of, and research priorities needed to advance the field for, the four most advanced

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AD BBMs, including amyloid-beta 42/amyloid-beta 40 (Aβ42/Aβ40), phospho-tau (p-tau), neurofilament light (NfL), and glial fibrillary acidic protein (GFAP), as well as potential combinations of markers. These recommendations call for real-world studies on the robustness of plasma Aβ42/Aβ40 as a diagnostic test for cerebral Aβ pathology as well as head-to-head studies comparing the performance of different forms of p-tau in different clinical contexts and across disease stages (1). BBMs should be developed, validated and prospectively analyzed in large, diverse and independent cohort studies to understand their reliability and predictiveness across a variety of individuals, groups and populations.

There is a need to streamline the approach of BBMs into primary care for individuals entering the system with cognitive concerns and/or cognitive complaints, but also to decrease the burden on already strained specialists in this field. These tools have the potential to advance the diagnostic and treatment process for all patients, but the recommendation today is that they should not be used by clinicians who do not have the necessary expertise nor should they be used in isolation of other available tools. Rather, they must be part of an integrated approach to diagnosis, treatment and care decisions. Angioni et al appropriately highlight that "The disclosure of BBM results is likely to have a major impact for some patients and care partners," (2) and it will be critical to comprehensively train and guide providers on test implementation, interpretation and disclosure of results. While BBMs for AD may provide cost-effective, non-invasive and globally scalable options for patient care, patients also deserve reliable and evidence-based results to be able to make informed decisions about their health.

Disclosures: Maria C. Carrillo is a full-time employee of the Alzheimer's Association. She has a daughter that is a full-time graduate student in the USC Neuroscience program. Heather M. Snyder is a full-time employee of the Alzheimer's Association. Rebecca M. Edelmayer is a full-time employee of the Alzheimer's Association.

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