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Editorial

What Are the Remaining Challenges before Blood-Based Biomarkers for Alzheimer's Disease Can Be Used in Clinical Practice?

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At a time when the widespread use of disease modifying therapy (DMT) seems imminent, one of the remaining key challenges in the field of Alzheimer's disease (AD) is to get these DMTs to everyone who needs them by providing a timely and accurate diagnosis (1).

In a specialist setting, highly accurate cerebrospinal fluid (CSF) tests and positron emission tomography (PET) are used to detect underlying amyloid and tau pathology as an aid in diagnosis. These tests come with limitations around global availability, high costs, lack of reimbursement, and perceived invasiveness. Another major hurdle towards a timely and accurate AD diagnosis is the bottleneck of insufficient available specialists to perform an AD diagnosis, especially when DMT becomes widely available (1).

To overcome these limitations, blood biomarkers (BBMs) have been proposed as minimally-invasive, easily accessible, globally scalable, and cost-effective triaging tests to be used early in the diagnostic pathway before confirmation of AD pathology via CSF or PET testing (2, 3). BBMs have the potential to increase the efficiency of the AD diagnostic pathway by fast-tracking people with expected underlying AD pathology to a timely confirmation of amyloid pathology via CSF or PET which is a prerequisite for anti-amyloid therapy administration (2).

Ever since the groundbreaking discovery in 2017 (4 and 5), that brain derived AD related proteins can in fact be measured in blood and that these proteins have utility as diagnostic biomarkers, the field has moved with tremendous speed to discover additional BBMs, developed highly sensitive methods to measure them, and to bring them to the clinic as fast as possible. However, there are still some key steps on the way to enable the widespread implementation and adoption of BBMs in clinical practice:

To date, the vast majority of data on BBMs has been generated using retrospectively measured banked blood samples collected in well-controlled study settings in populations of European descent. Using banked samples is usually the first logical step in assessing the diagnostic value of newly discovered biomarkers. However, it can have major limitations in translatability to a real-world setting. For example, in clinical routine, the preanalytical sample handling is usually less well controlled and the study populations are ethnically more diverse and heterogeneous when it comes to comorbidities. So three key questions remain to be answered:

1. Does the promising clinical performance of BBMs reported so far hold up in populations that more accurately reflect a real-world setting with higher variability in sample handling and testing as well as heterogeneity across patients?
2. Will the clinical performance of BBMs in a routine setting result in actionable information that helps clinicians to advise patients meaningfully?
3. Will cutoffs be uniformly applicable across different populations, ethnicities, and disease stages that potentially have varying prevalences of amyloid PET/CSF positivity and different distributions of BBM levels?

In order to answer these questions, we need to conduct large-scale prospective studies to compare BBM cutoffs and clinical performance across an ethnically diverse and heterogeneous patient population.

Another important next step is to better understand the utility and challenges in the implementation of BBM in primary vs. speciality care. While historically biomarker testing for amyloid pathology has been conducted by specialists, the main benefit of BBMs in making the diagnostic pathway more efficient might lie in deploying them in primary care as triaging tests to alleviate the bottleneck of insufficient specialist visits (2). However, recently published appropriate use recommendations for BBMs in AD do not support their widespread use in primary care just yet (3) since this would require more data and consideration:

1. What information from a BBM test would be considered actionable and meaningful for primary care physicians and how to disclose it to the patient?
2. Can the clinical performance of current BBMs live up to the expectations of primary care physicians when it comes to their clinical utility?

In order to answer these questions, we must closely involve primary care physicians in the discussions about BBM implementation, disclosure and education and must

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conduct studies in primary care populations to evaluate the utility of BBMs in that setting.

Today, BBMs are already being used to increase the cost-effectiveness and speed of clinical trial recruitment (mainly in secondary prevention studies like AHEAD, SKYLINE, TRAILBLAZER-ALZ3). They are also being measured as exploratory pharmacodynamic biomarkers to evaluate the treatment response of pharmacological interventions. On a smaller scale, BBMs are also used in the clinic outside of trials as lab developed tests (LDTs). However, no AD BBM has been approved by the FDA as an in vitro diagnostic (IVD) for use in routine practices yet. Like in many other disease areas, IVD approval will allow large lab providers and hospitals to easily implement BBMs in their offering to physicians and patients, which will enable rapid and global scalability. Regulatory approval as an IVD is also the basis for establishing clinical utility and reimbursement. In consequence, an approved IVD will trigger the widespread use and adoption in clinical routine because labs, physicians, payors, and patients can trust that the technical and clinical performance of a BBM lives up to its intended use.

Current BBMs are a promising first step in transforming the diagnostic pathway towards a timely, equitable and accurate diagnosis of AD but they are also not the last step. The clinical performance of current BBMs allows for their use as triage tests before subsequent confirmation of amyloid pathology by CSF or PET testing and a clinical diagnosis, which is of great value. But they are not yet accurate enough to replace CSF and PET testing (3). Eventually, replacing CSF and PET testing with a simple BBM would be most impactful since it would remove most of today's limitations of CSF and PET testing in a specialist setting. In order to get there, the field needs to continue to discover new biomarkers or combinations of biomarkers that increase the clinical performance of current tests while bringing current triaging BBMs to the clinic as fast as possible. These new biomarkers do not necessarily have to be blood-based, they could also utilize other technologies as long as they are minimally-invasive, easily accessible, globally scalable, and cost-effective (e.g. digital biomarkers, retina imaging, non-protein based blood tests, etc.).

It took more than two decades for AD CSF and PET testing to evolve from biomarker discovery to FDA approval and subsequent implementation in clinical routine, even if not yet as widespread as desired. The hope is that we can achieve this much faster for BBMs to democratize a timely, equitable and accurate AD diagnosis for everyone in the world who needs it.

The EU/US CTAD taskforce met in May 2022 to discuss these open questions and to help pave the way to get BBMs to the clinic faster (6).

Conflict of interest: Dr. Bittner is a full time employee of F.Hoffmann-LaRoche and Genentech and owns stock options in F.Hoffmann-LaRoche.

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