J Prev Alz Dis 2022;4(9):565-566
Published online October 16, 2022, http://dx.doi.org/10.14283/jpad.2022.88

Editorial

Blood-Based Biomarkers for Alzheimer's Disease: Are We There Yet?

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Angioni et al (1) provide a topical and thorough report from the 2022 EU/US CTAD Task Force on "what must be done" to move blood-based biomarkers (BBMs) of Alzheimer's disease (AD) from research to use in clinical practice. There is little doubt that «timely and accurate diagnosis of Alzheimer's disease in clinical practice» (1) is an important goal. Biomarker results can assist with prognostication and may be used more widely in the future to select, as in the case now for aducanumab in the US, and possibly monitor, therapies. On the other hand, as the authors note, the consequences of misdiagnosis include incorrect or suboptimal treatment, delayed treatment, provision of incorrect information regarding what disease is present as well as its prognosis, and, I would add, missed research opportunities. Non-invasive and inexpensive biomarkers, that can be measured serially, will represent a very important advance for our field. The goal of this opinion piece is to highlight some of the key themes from the report as well as point out some potentially important caveats. What is the punchline? There have been dramatic gains in the development of AD BBMs from careful studies in multiple laboratories around the world, which could fuel speculation that clinical application of these AD BBMs is imminent. The authors suggest, and I agree, that this is premature. We have many bridges to cross.

What are some of the issues? The authors and other experts delineate multiple steps that will be required for clinical application of AD BBMs. For example, Frisoni et al (2) describe a five-phase developmental framework: 1) initial exploratory studies, 2) clinical assay development and validation, 3) study of biomarkers and retrospective in longitudinal cohorts followed by 4) evaluation in prospective validation studies in real world settings. Phase 5 is focused on the details of clinical implementation. Teunnissen et al (3) and others have suggested that phases 1 and 2 of this roadmap have been substantially addressed for the best-studied AD BBMs measuring Abeta, pTau, and NFL, whereas GFAP is still in phases 1 and 2, and that all AD BBMs still need to progress through phases 4 and 5. We lack standardized operating procedures for processing and storage as well as other pre-analytical factors, which may have differential effects on different biomarkers. These factors are being mapped as part of the Global Biomarker Standardization Consortium (4). In order for assays to be deployed in clinical practice, cost-effective and scalable assays will need to be developed and approved by certifying authorities and hopefully covered by payors.

Which biomarker(s) should be used, and how? As noted above, we have measures of amyloid, different pTau species, neurodegeneration, and inflammation, for example, mainly derived from retrospective studies of non-representative research cohorts, analyzed in large batches with optimized thresholds based on large batches. Different individual tests may have different performance characteristics when used alone versus the performance of a combination of biomarkers. We don't know which combination is best, the detailed pros and cons of incorporating APOE genotyping, or of incorporating cognitive assessment. Some of these biomarkers are influenced, sometimes differentially, by important other variables such as age, sex, ethnicity, APOE genotype, renal disease, heart disease, vascular disease, body mass index, and/or hypertension. Stage of illness may matter a great deal: there is evidence suggesting that different BBM's perform differently, alone or in combination, in preclinical, MCI and dementia stages of AD. Under what circumstances would it make sense to even conduct testing in presymptomatic stages of AD? We need more information about what threshold to use based on prospective longitudinal studies. Importantly, these studies, which have not yet been conducted, need to be performed in the highly heterogeneous population that reflects real world patients, especially those in primary care. We have to agree on whether or not confirmation of blood test results is required, e.g., with CSF or PET. And then there are tomorrow's promising AD biomarkers, such as improved measures of the current cardinal aspects of AD pathology as we as BBMs addressing other aspects of AD, such as synaptic or membrane dysfunction or microglial activation. Such new BBMs could be compelling but will need to be vetted. Finally, all of this addresses just AD pathology, but negative results regarding AD pathology don't preclude other pathologies, e.g. TDP 43, alpha synuclein, vascular burden, trauma, etc. We should anticipate the emergence of new BBM's for other proteinopathies, which will add further complexity to clinical application. All of these nuances argue for the development of clinical practice algorithms and appropriate use criteria that cannot be created in the near

Received September 11, 2022
Accepted for publication September 18, 2022

term because we have insufficient evidence and that in any case will likely need to be updated reiteratively.

Suppose all of this is accomplished and we are technically ready to deploy in the clinic. Who will be qualified to perform the pretest pre-and post-testing counseling? Some suggest that this should be the purview of specialists, although Angioni et al make a good case for involving our primary care colleagues (1). Should others besides the patient be involved, such as family members or other loved ones? The pre-counseling will need to address the nature of the test, the goals of testing, possible outcomes, risks (e.g., such as threats to health or life insurance, stigma,) implications for blood relatives, limitations, and alternatives. Perhaps standards need to be developed to assess appropriateness of disclosure of this information, e.g., for psychologically vulnerable individuals. When it comes to actual disclosure, exactly how will we explain risk, prognosis, and genetic implications? How will the information be used to guide treatment selection? How will negative results be addressed? As noted above, negative Alzheimer's pathology results don't preclude other pathologies. And what if a combination of tests is used and there are discordant results? Published guidelines are emerging (e.g., 5), but there is more to be done.

In view of all of these considerations, Teunissen et al (3) suggest that the use of AD BBMs in clinical practice is a "few years" away (3); Angioni et al (1) also state as much. In the meantime, however, AD BBMs are already transforming both symptomatic and preventative AD clinical trials. They are being used to: enrich for elevated brain amyloid, select participants for AD trials or to exclude them from trials in other brain diseases, for pharmacodynamic studies, and monitor treatment, and perhaps they can be used eventually as therapeutic surrogates. As Agnoni et al. put it, "Their widespread use should quickly bring dramatic improvements to the conduct of these trials, facilitating recruitment, reducing time and costs, and increasing the prospect of effective treatments for the disease." We are already "there" in the clinical trials arena; we have much to accomplish before they are ready for routine use in the clinic. The furious pace of their development thus far augurs well for the future.

Conflict of interest: Dr. Tariot reports grants from NIA, other from Adamas Pharmaceuticals, personal fees and other from Abbvie, personal fees from AC Immune, personal fees from Acadia, personal fees from Athira, personal fees from Axsome, personal fees from BioXcel, personal fees and other from Cortexyme, personal fees from Eisai, personal fees and other from Genentech, personal fees and other from Merck, personal fees from Novo Nordisk, personal fees from Syneos, personal fees from T3D Therapeutics, personal fees and other from Biogen, other from Eli Lilly, other from Novartis, other from Roche, personal fees from Otsuka & Astex, outside the submitted work; In addition, Dr. Tariot has a patent U.S. Patent # 11/632,747, «Biomarkers of Neurodegenerative Disease» issued.

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How to cite this article: P. Tariot. Editorial: Blood-Based Biomarkers for Alzheimer's Disease: Are We There Yet? J Prev Alz Dis 2022;4(9):565-566; http://dx.doi.org/10.14283/jpad.2022.88