J Prev Alz Dis 2023;3(10):418-425
Published online June 13, 2023, http://dx.doi.org/10.14283/jpad.2023.68

CTAD Task Force Paper

Can We Use Blood Biomarkers as Entry Criteria and for Monitoring Drug Treatment Effects in Clinical Trials? A Report from the EU/US CTAD Task Force

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Abstract

In randomized clinical trials (RCTs) for Alzheimer's Disease (AD), cerebrospinal fluid (CSF) and positron emission tomography (PET) biomarkers are currently used for the detection and monitoring of AD pathological features. The use of less resource-intensive plasma biomarkers could decrease the burden to study volunteers and limit costs and time for study enrollment. Blood-based markers (BBMs) could thus play an important role in improving the design and the conduct of RCTs on AD. It remains to be determined if the data available on BBMs are strong enough to replace CSF and PET biomarkers as entry criteria and monitoring tools in RCTs.

Key words: Alzheimer's disease, randomized clinical trials, screening, monitoring, amyloid, tau.

Introduction

The field of blood-based markers (BBMs) in Alzheimer's Disease (AD) is rapidly evolving and demonstrating increasingly promising performance (1, 2). The state of scientific development of BBMs (i.e. amyloid-beta isoforms, phosphorylated tau species, combined markers and algorithms) and the next steps needed before their implementation in clinical practice have been discussed in the virtual meeting of the CTAD Task Force which took place in May 2022 (3). Following the encouraging results of Clarity AD trial (4), we have arrived at a pivotal moment for the development of new therapeutic strategies to prevent and delay AD progression. In this context, BBMs could play a central role in improving the design and the conduct of randomized clinical trials (RCTs) on AD (5). Positron emission tomography (PET) and cerebrospinal fluid (CSF) analysis are now well-accepted strategies for the detection and monitoring of AD pathological features. However, PET is costly (e.g. the average amyloid PET cost in US is between 5000 and 7000 dollars), time-consuming, inconvenient (e.g. logistic requiring scanner and tracer timing), and not easily accessible outside of the major metropolitan areas. In addition, widespread use of CSF biomarkers could be problematic due to the expertise needed to perform a lumbar puncture and the invasive nature of sample procurement. The use of less resource-intensive markers as BBMs, potentially able to

Received April 17, 2023
Accepted for publication May 22, 2023

Table 1. Some examples of BBMs use in clinical trials as entry criteria

PRE-SCREENING						
Study	**Clinicaltrial.gov Identifier**	**Phase**	**Population**	**Drug**	**BBM**	**Confirmatory Exam**
AUTONOMY	NCT04619420	II	Early symptomatic AD	JNJ-63733657	p-tau217	Tau PET
INVOKE-2	NCT04592874	II	Early symptomatic AD	AL002	PrecivityAD™ (algorithm derived from Aβ 42/40, ApoE and Age)	Amyloid PET or CSF
PROSPECT-ALZ	NCT05063539	II	Early symptomatic AD	LY3372689	p-tau217	Amyloid PET Tau PET
TRAILBLAZER-ALZ 2	NCT04437511	III	Early symptomatic AD	Donanemab	p-tau181	Amyloid PET Tau PET
AHEAD 3-45	NCT04468659	III	Preclinical AD	Lecanemab	Aβ42/40 ratio	Amyloid PET
SKYLINE	NCT05256134	III	Preclinical AD	Gantenerumab	p-tau181 and ApoE	Amyloid PET or CSF
SCREENING						
Study	**Clinicaltrial.gov Identifier**	**Phase**	**Population**	**Drug**	**BBM**	
TRAILBLAZER-ALZ 3	NCT05026866	III	Preclinical AD	Donanemab	p-tau217	

identify the presence or the absence of the drug target (i.e. amyloidopathy, tauopathy, neurodegeneration, or other) could reduce the cost and burden for the study volunteers, and promote the speed of enrollment (6). Within this framework, some clinical trials are already using BBMs for pre-screening or screening procedures and to monitor the pharmacological effects of the study drug (3). However, it remains to be determined whether the data on BBMs performance available thus far are robust enough to justify BBMs to replace PET and CSF biomarkers as entry and monitoring criteria in RCTs. In order to address these issues, the International CTAD Task Force met in San Francisco on November 29th 2022. Specifically, the CTAD Task Force assessed:

1. The use of BBMs as entry criteria in recent and ongoing RCTs
2. Issues related to the use of BBMs as entry criteria
3. The use of BBMs as monitoring criteria in clinical trials
4. Issues related to the use of BBMs as monitoring criteria
5. The next steps and research prospects for BBMs in clinical trials

Short presentations reflecting the perspectives of academia, pharma industry and assay industry were followed by general discussions. Key points are summarized in Tables 2 and 4.

The use of BBMs as entry criteria in clinical trials

BBMs can be used in clinical trials as pre-screening tools, to rule out participants that are not likely to have pathological features of AD. The use of BBMs does reduce the number of confirmatory exams such as PET (amyloid and/or tau) or CSF analysis needed to corroborate the presence of the study drug target in a given patient. Several ongoing and past clinical trials used BBMs with this aim as documented in the Table 1.

The TRAILBLAZER-ALZ 2 is a phase 3 study designed to evaluate the safety and efficacy of donanemab in early symptomatic AD individuals with confirmed amyloid and intermediate or high tau pathology (7). In this trial, Simoa p-tau181 was explored as a pre-screener. In the early version of the protocol, the positivity of p-tau181 was required before proceeding to amyloid or tau PET. An intermediate analysis has shown that among the 752 patients selected using p-tau181 as a pre-screener, 63 % presented with positivity on both amyloid and tau PET. In contrast, considering 3619 patients screened directly using PET measures, the percentage of individuals with both amyloid and tau PET positivity was markedly lower (37 %) (8). These results indicate that the use of p-tau181 as a pre-screener could reduce screen fails due to amyloid and tau PET negativity and the costs related to PET procedures in clinical trials.

The Janssen Simoa p-tau217 assay is used in the AUTONOMY clinical trial which enrolls individuals with MCI and mild dementia due to AD having a positive tau PET with an intermediate tau burden as a pre-screening tool. Participants with plasma p-tau217 tau levels ≥ of 0.1 pg/ml are allowed to carry on screening procedures with tau PET. An intermediate analysis of 346 patients has shown that 86% of patients with p-tau217 levels above the threshold were tau PET positive and 64% presented an intermediate tau burden (9). Janssen p-tau217 showed excellent performance in predicting amyloid (10, 11, 12) and tau status (13). Janssen p-tau217 might be potentially able to stratify tau pathology and identify early AD participants for anti-tau trials.

Similar results were found in the PROSPECT-ALZ clinical trial, designed to assess the safety and efficacy of the LY3372689, an O-GlcNAcase (OGA) inhibitor, in an early symptomatic AD population. In this trial, considering individuals for which tau PET results are available, 57 % of patients presenting with p-tau217 values above the pre-screening threshold were eligible for randomization following positivity of tau PET

(intermediate/high burden) (14).

The plasma amyloid-beta (Aβ) 42/40 ratio, measured using C2N Diagnostics' liquid chromatography with tandem mass spectrometry (LC-MS/MS) Precivity™ platform, is used to identify participants not likely to have elevated amyloid levels in the AHEAD 3-45 study. The AHEAD 3-45 study consists of two different trials aimed to assess whether lecanemab can prevent cognitive decline and slow tau accumulation in cognitively unimpaired individuals with intermediate (i.e. A3 cohort) and elevated (i.e. A45 cohort) amyloid burden (15). Definitive eligibility for randomization is based on amyloid PET (15).

The INVOKE-2 study is a phase 2 clinical trial designed to assess the efficacy and safety of AL002 in participants with early AD. This study offers an example of the use of a multi-analyte blood test, the PrecivityAD™ test, as a pre-screener (16). PrecivityAD is a validated clinical test that uses C2N's mass spectrometry methods to generate the Amyloid Probability Score (APS), an algorithm output derived from the combination of the plasma Aβ42/40 ratio, Apolipoprotein E (ApoE) proteotype (i.e. inferred genotype) and the patient's age (17). The APS reflects the likelihood that an individual being amyloid positive on amyloid PET scan in a scale from 0 to 100. In the INVOKE-2 study amyloid positivity must be confirmed via amyloid PET or CSF analysis.

BBMs can also be used as screening tools in clinical trials for which, in case of the positivity of BBMs, confirmation by PET or CSF analysis is not required. In contrast to their widespread use as pre-screeners, the use of BBMs as screening tools is currently limited to Eli Lilly's ongoing TRAILBLAZER-ALZ 3 trial, designed to assess the efficacity of donanemab in pre-clinical AD (18).

Issues related to BBMs use as entry criteria

Is concordance with PET and CSF measures high enough?

Currently, CSF markers (e.g. p-tau/Aβ42 or Aβ42/40) and amyloid PET are used interchangeably as entry criteria in AD clinical trials. The neuropathological confirmation by post-mortem examination of Aβ plaques and tau neurofibrillary tangles remains the gold standard for a definitive AD diagnosis (19, 20). While neither CSF analysis or amyloid PET is a true gold standard, they show high concordance with autopsy diagnosis in classifying patients as amyloid positive or negative. This suggests that both CSF and amyloid PET methods effectively capture the underlying amyloid pathology. Multiple BBMs assays have been validated with neuropathological data (21-26). However, other BBMs assays use amyloid PET and CSF as reference standard, thus already limiting their performance metrics due to some errors in PET and CSF assessment. For example, if PET has false negative results, then BBMs may appear artificially higher false positives. For BBMs to replace amyloid PET or CSF, neuropathologic confirmation for these measures is required. In the absence of validation with autopsy data, for BBMs to replace amyloid PET or CSF, a very high predictive value for these measures is needed.

Recent studies suggest that both plasma p-tau markers (specifically p-tau217 and p-tau181 and ratios to their non-phosphorylated forms) and plasma Aβ42/40 assays measured with optimized mass spectrometry-based (MS) methods reach the required high performance in head-to-head studies (10, 12, 27). However, the performance can vary greatly depending on the specific biomarker and assay used with AUCs ranging from 0.65 to 0.96 (10, 12, 27). Combining two BBMs (e.g. Aβ42/40 and p-tau/t-tau) or a single BBM with other clinical factors (e.g. age or ApoE) has been shown to increase the performances (17, 28, 29). To perform well as a screening tool, BBMs should be longitudinally stable at the patient level and over time with limited variance (test-retest variance and variance over time). Plasma Aβ42/40 immunoassays have shown variable results across studies (30). It has been demonstrated that the small difference in immunoassays of Aβ42/40 between PET amyloid positive and negative subjects can result in a lack of robustness (e.g. caused by pre-analytical differences) and reduced clinical performance in less controlled settings (31, 32). The mass spectrometry measurements of Aβ42/40 appear to have greater AUC to predict amyloid PET or a positive CSF profile than immunoassays (30). The analytical stability of these measures appears adequate, with cut point value stability across multiple independent cohort studies (17, 33). More extensive validation of current BBMs will take place in the future and is essential to expand their use in clinical trials. Larger studies are needed to fully characterize BBMs performance and determine for each assay (or combination of assays) whether its concordance with PET and/or CSF performances is high enough to suffice as standalone entry criteria for future clinical trials. However, AUCs approaching 0.95 for several BBM methods versus CSF and amyloid PET (10, 12) suggest feasibility. It is noteworthy that this high level of performance to well-accepted reference standards for amyloid assessment is similar to the performance of CSF relative to PET that was required to achieve recent FDA-clearances of several CSF tests.

Confounding factors and optimal cut points

Currently, cut points are derived from data of previous repositories of plasma collected from patients who have had a PET. It is important to underscore that these cut points were generally established for most assays in research populations (i.e. in most of cases well-educated, White population, with few comorbidities). It remains to be determined whatever various clinical variables (e.g. age, comorbidities, kidney function, drugs, race/ethnicity

Table 2. Key points about BBMs use as entry criteria for Alzheimer's trials

- Promising feedback for BBMs as pre-screeners but limited experience for BBMs as screening tools.
- Advantages of BBMs use:
  - Lower costs for enrollment if pre-screening is done with BBMs, since less screening failures occur with amyloid PET or CSF analysis
  - BBMs can promote enrollment speed and reduce burden for study participants
  - A blood sample for a BBM can be obtained in a home setting.
- Gaps to be resolved:
  - Limited knowledge of confounding factors, potentially able to modify BBMs values
  - Cut points established from previous repositories of plasma collected from research patients may not be applicable in more diverse populations.

and cognitive co-pathologies) need to be considered in the interpretation of BBMs levels. Several comorbidities, like ischemic heart disease, stroke, chronic kidney disease, were associated with higher plasma p-tau181 and p-tau217 levels in the Mayo Clinic Study of Aging cohort (34). In the same cohort, chronic kidney disease was also associated with higher levels of plasma Aβ40, Aβ42 and Aβ42/40 ratio measured by Simoa immunoassays (35). In BioFINDER1 and 2 cohorts, creatinine and BMI were associated with Aβ42 and Aβ40 values but not with the Aβ42/40 ratio (36). The mechanism by which comorbidities are associated with changes in cut points is currently unclear. It is unclear if cut points should be adjusted for comorbidities. Furthermore, the prevalence of amyloid positivity has been reported to be lower in Black and other underrepresented populations than in the White population (37). These changes could reflect underlying biology, sampling bias, or other factors. In clinical trials the optimal cut points should account for metrics like positive and negative predictive values (i.e. proportion of patients that are plasma positive/negative and would also be positive/negative with PET). The predictive values depend on the amyloid positivity prevalence in the study population, and reaching high positive predictive values in low prevalence settings requires very high performance of plasma assays. In some settings and using some assays, it has been shown that BBMs may only be useful for ruling out amyloid pathology, while confirmation of amyloid positivity by PET may still be needed in cases tested positive with the plasma biomarker. It is important to note that optimizing for a high positive predictive value (i.e. by using a more extreme cut-off) may exclude a large number of subjects that would have been eligible with amyloid PET, therefore increase the number of patients who need to be screened for a trial, and finally bias the study population (e.g. compared to the population that would have been enrolled with amyloid PET).

The use of BBMs as monitoring criteria in clinical trials

BBMs can be used in clinical trials to assess changes in response to treatment. Due to their well-known properties (i.e. widely accessible, non-invasive, less time-consuming, less expensive), BBMs offer the advantage to be performed more frequently than PET, improving the temporal resolution of monitoring. On the other hand, BBMs do not indicate the neuroanatomic distribution of AD pathology. The main results regarding BBMs use in clinical trials as monitoring criteria are summarized in the Table 3. In the EMERGE and ENGAGE trials, a reduction in plasma p-tau181 levels at week 78 was observed in individuals treated with high doses of aducanumab. Reduced p-tau181 values were correlated with reductions in amyloid PET and with clinical efficacity outcomes (e.g. weak associations with CDR-SB, MMSE, ADAS-COG and ADCS-ADL-MCI scores) in both trials (38). In the BAN2401-G000-201 core trial dose-dependent changes in BBMs (i.e. reduction for p-tau181 and increase Aβ42/40 ratio) were observed in patients treated with lecanemab. These changes were associated with reductions in brain amyloid burden as measured by PET and less cognitive decline over a period of 18 months (39). Interestingly, during the gap period that followed the core phase and preceded the open-label extension (OLE), BBMs tended to return to pre-randomization levels more quickly than amyloid PET: Aβ42/40 decreased by 47%, plasma p-tau181 rose by 24%, while the increase in amyloid burden measured by PET was estimated at 6 centiloids (39). This might suggest that BBMs are more sensitive measures of amyloid re-accumulation compared to amyloid PET. Similar results were found in the phase 3 Clarity AD study (i.e. p-tau181 and glial fibrillary acidic protein reduction and Aβ42/40 increase in the lecanemab arm, with a significant difference with placebo) and the OLE of gantenerumab phase 3 trials Scarlet RoAD and Marguerite RoAD (i.e. reductions in p-tau181 and p-tau217 and increase of Aβ42/40 ratio over 3 years) (4) (40). In a secondary analysis from the TRAILBLAZER-ALZ trial a reduction in plasma p-tau217 and glial fibrillary acidic protein (GFAP) was found in patients treated with donenemab compared to placebo with no significant difference in neurofilament-light chain (NfL) and Aβ42/40 levels between the two arms (41). In this trial, the reduction of p-tau217 and GFAP persisted until the end of the study even in individuals who interrupted the treatment at week 24 following the achievement of targeted amyloid reduction. In TRAILBLAZER-ALZ only changes in NfL showed a significant association with

Table 3. Some examples of BBMs use in clinical trials as monitoring criteria

	Clarity AD	Emerge	Engage	Scarlet Road	Marguerite Road	Trailblazer ALZ	Trailblazer ALZ 4	ALZ-801-201-ADBM
	NCT03887455	NCT02484547	NCT02477800	NCT01224106	NCT02051608	NCT03367403	NCT05108922	NCT04693520
	Lecanemab	Aducanumab		Gantenerumab		Donanemab	Donanemab versus Aducanumab	ALZ-801
	Phase 3	Phase 3		Phase 3 OLE		Phase 2	Phase 3	Phase 2
Aβ 42/40	Increased ** from BL to mo18			+14% from OLE BL to mo36	+9% from OLE BL to mo36	+ 4 % * from BL to w76		
p-tau181	Reduced ** from BL to mo18	-13 % ** from BL to w78	- 16 % ** from BL to w78	-13 % from OLE BL to mo36	-7 % from OLE BL to mo36			-41% from BL to w52
p-tau181/ Aβ42								-37 % from BL to w52
p-tau217		-	-	-24% from OLE BL to mo36	-11% from OLE BL to mo36	-23% ** from BL to w76	Donanemab -25% Aducanumab+2.8% from BL to w24	
GFAP	Reduced ** from BL to mo18					-12% ** from BL to w76		

BL, baseline; mo, months; OLE, open label extension; w,week; * no significant difference with placebo arm, ** significant difference with placebo arm

clinical efficacity outcomes (i.e. iADRS). P-tau217 was also used as an exploratory outcome in the TRAILBLAZER-ALZ 4 study which compared donanemab to aducanumab on amyloid plaque clearance in people with early symptomatic AD. Individuals treated with donanemab received 700 mg Q4W for the first 3 doses and the full dose of 1400 mg Q4W thereafter. The full dose of aducanumab (10 mg/kg Q4W) was reached after 24 weeks. In this trial, donanemab, but not aducanumab treatment significantly reduced p-tau217 values at 6 months (42). BBMs are also used as monitoring tools in trials considering other drugs than anti-amyloid antibodies (e.g. small molecules). In this context, in the ALZ-801 phase 2 trial, early AD individuals who are carriers of one or two copies of the ε4 allele of ApoE gene, treated with ALZ-801 presented a reduction in plasma p-tau181 and p-tau181/ Aβ42 levels from baseline to 12 months (43).

Issues related to BBMs use as monitoring criteria

BBMs as monitoring tools at study level

An optimal monitoring BBM to be used in clinical trials should present a large degree of changes during the natural history of AD. Changes in BBMs should be specifically due to AD pathology (and not to other factors). A recent analysis from the BioFINDER cohort showed that plasma p-tau217 had longitudinal increases over a period of 4-6 years in amyloid-positive individuals, with no such changes demonstrated in p-tau231, p-tau181, Aβ42/40, GFAP or NfL that reached a plateau (44). In this study, longitudinal increases of p-tau217 were also associated with declining cognition and brain atrophy in typical AD signature regions. These results were replicated using data from the Wisconsin Registry for Alzheimer's Prevention.

To be useful as a monitoring tool in RCTs, BBMs values should reflect the drug-induced changes in brain (i.e. reduced AD features as amyloid and tau burden). Recent RCTs (4, 38, 41) have shown that individuals treated with anti-amyloid drugs presented significant differences in BBMs values if compared to placebo (Table 3). However, BBMs levels were not completely "normalized" in the treatment arms to levels of age-matched people without AD. Moreover, it is important to consider that drugs might affect their target differently in the periphery and in the brain. Therapeutic antibodies may alter the half-life of their target in plasma, where large amounts of therapeutic antibodies bind small amounts of amyloid, making the data difficult to interpret. For example, solanezumab was found to inhibit serum-induced degradation of Aβ (45), and anti-tau antibodies to prolong the half-life of tau in blood (46). A potential solution might be to measure a brain-specific protein in blood that is downstream of the drug target instead of the drug target itself (e.g. plasma p-tau in case of anti-amyloid therapy).

Finally, a suitable BBM should not be confounded by other hallmarks of the disease. For example, in case of a monitoring BBM for amyloid, the BBM values should not be impacted by changes in tau pathology. In this case, changes induced by tau pathology but not amyloid pathology could confound the utility of a BBM as a monitoring marker of amyloid. Plasma p-tau species seem to be associated with amyloid and tau pathology (21). This needs to be further investigated.

BBMs as monitoring tools at individual level

BBMs have the potential to provide deterministic qualities at the individual level. If BBMs are validated as monitoring tools at individual level, in AD patients treated with disease-modifying drugs, the monitoring of treatment effects using BBMs may allow dose

Table 4. Key points about BBMs use to monitor treatment effects in Alzheimer's trials

- BBMs can be performed more frequently than PET due to no radiation burden, permitting to improve the temporal resolution of monitoring.
- BBMs cannot inform about the neuroanatomic evolution of AD pathology.
- Multiple BBMs covering neurodegeneration, neuroinflammation and neuropathology, can be assessed based on one blood draw.
- BBMs have mainly been used as exploratory outcomes in AD clinical trials so far.
- More evidence that drug-induced changes in BBMs values are consistently correlated with beneficial changes in clinical outcomes is required to use BBMs as surrogate endpoints in clinical trials.
- Characteristics of an optimal monitoring BBM:
  - Longitudinal change of BBM concentration is associated with changes in underlying pathology
  - BBM values reflect the drug-induced changes in brain
  - At the individual level, changes in BBM could allow treatment to be tailored (e.g. lower/greater doses or frequency, decision to start/stop treatment).

modification (e.g. less/more frequent or lower/higher dose), discontinuation, switching to other drugs or combinations of drugs. Several BBMs can be considered for this use. Plasma Aβ42/40 has a narrow dynamic range between normal and abnormal, which puts limits on therapeutic response for assays without sufficient precision, particularly at the individual level. NfL is an interesting candidate to monitor the effects of pharmacologic treatments in individuals presenting neurologic diseases involving large myelinated fibers as Multiple Sclerosis and Amyotrophic Lateral Sclerosis (47, 48), but evidence in AD field is lacking at this time. GFAP is a marker of astroglial activation and astrocytosis, non-specific for AD. This could represent a limitation for its use to guide decisions at an individual level. P-tau species look promising but more data are needed to identify and validate for each assay the thresholds corresponding to significant outcomes such as amyloid removal and clinical benefit.

The next steps and research prospects

We are at a turning point in establishing the validity and utility of BBMs in clinical trials as entry criteria. BBMs increase promise and might permit to limit costs, time and complexity of enrollment procedures. However, further research is needed to fully characterize the performance and robustness of BBMs in more diverse populations and settings before they can be considered definitively a substitute for PET imaging or CSF testing as entry criteria. There is an urgent need for standardization of operating procedures to reduce the sources of variability. The question regarding the optimal cut points for each assay is still open and will depend on the specific context of use. More results from samples obtained prospectively are needed to validate, or possibly change, the current cut points. It is extremely desirable to use BBMs to monitor treatment response at a study level, and at a patient level to tailor treatments as is currently done for oncology. BBMs have been mainly used as exploratory outcomes in AD clinical trials so far. More evidence that drug-induced changes in BBMs values are consistently correlated with beneficial changes in clinical outcomes is required to use BBMs as surrogate endpoints in clinical trials. It will be important to understand the extent to which BBM concentrations need to be normalized to be consistently associated with a clinical benefit.

A future goal could be the development of new BBMs having the potential to be used in clinical trials. The AlzoSure® Predict test quantifies the AZ284, a peptide of an unfolded variant of the p53 protein (49). In one study, the AlzoSure test was able to predict cognitive decline to AD-dementia with an AUC > 90 %, regardless of the cognitive status of patients at the time of test. Successful replication in other large cohorts remains to be seen. Combining two or more BBMs may help to increase the accuracy of BBMs. In this context, a new version of the C2N PrecivityAD test (i.e. PrecivityAD2) has been recently developed (50). The PrecivityAD2 combines the measure of the Aβ42/40 ratio and p-tau217 ratio (i.e. tau protein phosphorylated at amino acid 217/tau protein not phosphorylated at amino acid 217) to obtain a probability score reflecting the likelihood for a patient to be amyloid positive at PET. The PrecivityAD2 showed increased performance (compared to the previous version) with an AUC of 95% and an accuracy of 90% to detect amyloid positivity. Combining a Simoa multiplex of Aβ42/40, GFAP, NfL, together with pTau-181 was recently shown to give superior performance than any of the single biomarkers alone. Independent of age and ApoE status, this multi-marker test achieved an AUC of 91% for detecting amyloid positivity in cognitively normal subjects, and an AUC of 94% for detecting amyloid positivity among MCI patients (51).

BBMs development in RCTs as entry and monitoring criteria may ultimately enable their use in clinical practice when disease-modifying drugs are approved. BBMs have the potential to facilitate the management of disease-modifying drugs in clinical practice for patients, physicians and payers. BBMs will make RCTs more efficient and will facilitate knowledge transfer to clinical practice.

Conflict of interest: The Task Force was partially funded by registration fees from industrial participants. These corporations placed no restrictions on this work. D. Angioni is an investigator in clinical trials sponsored by Roche, Alector, Janssen, Alzheon, Otsuka, Novo Nordisk, UCB Pharma, Medesis Pharma Eisai,

Biogen and the CHU of Toulouse. No direct personal benefit is to be declared. O. Hansson has acquired research support (for the institution) from ADx, AVID Radiopharmaceuticals, Biogen, Eli Lilly, Eisai, Fujirebio, GE Healthcare, Pfizer, and Roche. In the past 2 years, he has received consultancy/speaker fees from AC Immune, Amylyx, Alzpath, BioArctic, Biogen, Cerveau, Eisai, Eli Lilly, Fujirebio, Genentech, Merck, Novartis, Novo Nordisk, Roche, Sanofi and Siemens. R. Bateman Washington University and Randall Bateman have equity ownership interest in C2N Diagnostics and Randall Bateman receives income from C2N Diagnostics for serving on the scientific advisory board. Randall Bateman may receive income based on technology licensed by Washington University to C2N Diagnostics. Randall Bateman has received research funding from Avid Radiopharmaceuticals, Janssen, Roche/Genentech, Eli Lilly, Eisai, Biogen, AbbVie, Bristol Myers Squibb and Novartis. Randall Bateman serves on the Roche Gantenerumab Steering Committee as an unpaid member. C. Rabe is a full-time employee of Genentech and owns stock options in F.Hoffmann-LaRoche. M. Toloue is an employee and shareholder in Quanterix Corporation. J.B. Braunstein is a full-time employee of and owns equity in C2N Diagnostics. Sam Agus is an employee of Diadem spA. J.R. Sims is an employee of Eli Lilly and Company: salary and minor stockholder. T. Bittner is a full-time employee of F.Hoffmann-LaRoche and Genentech and owns stock options in F.Hoffmann-LaRoche. M. Carrillo is a full-time employee of the Alzheimer's Association. She received lead grants (without funding) from NIA LEADS (Co-PI, non salaried). She has served on the scientific advisory board for San Antonio Alz Center EAB, ATRI/ACTC EAB and US POINTER Study DSM. She has a daughter that is a full-time graduate student in the USC Neuroscience program. H. Fillit received royalties from the Icahn School of Medicine at Mount Sinai. He is an unpaid consultant to Biogen. He has received consulting fees from Alector, Otsuka/Lundbeck, and LifeWork. He owns stock options in eFamilyCare. C.L. Master has nothing to declare. S. Salloway was the co-chair of the Investigator Steering Committee for the Aducanumab phase 3 program and he served as a site PI for the aducanumab and lecanemab phase 3 studies, the donanemab phase 2 trial and he was the Project Arm Leader for gantenerumab in DIAN-TU. He has received consulting income from Biogen, Lilly, Roche, Genentech, Bolden, Amylyx, Prothena and Eisai. He has no stock or royalties related to any medication in development. S. Salloway serves on the planning committee for the National Disease Modifying Treatment and Diagnostic Registry Work Group and he is a member of the ADRD Therapeutics Work Group. He is the first author for the report of ARIA in aducanumab phase 3 (Salloway, JAMA Neurology, 2022), the report of gantenerumab and solanezumab in DIAN-TU (Salloway, Nature Medicine, 2021). He is a co-author on the report of the donanemab phase 2 trial (Mintun, NEJM, 2021) and the Aducanumab Appropriate Use Recommendations (Cummings, Journal of the Prevention of Alzheimer's Disease, 2021). P. Aisen reports collaborations on the development of blood-based markers with C2N, Janssen and Roche, during the conduct of the study; grants from Lilly, Eisai, NIH, Alzheimer's Association; consultant fees from Merck, Biogen, Abbvie, Genentech, ImmunoBrain Checkpoint, Arrowhead, outside the submitted work. M. Weiner reports, outside the submitted work, grants from National Institutes of Health (NIH)/NINDS/National Institute on Aging (NIA), Department of Defense (DOD), California Department of Public Health (CDPH), University of Michigan, Siemens, Biogen, Hillblom Foundation, Alzheimer's Association, Johnson & Johnson, Kevin and Connie Shanahan, GE, VUmc, Australian Catholic University, The Stroke Foundation, Veterans Administration; personal fees from Boxer Capital, Cerecin, Clario, Dementia Society of Japan, Eisai, Guidepoint, Health and Wellness Partners, Indiana University, LCN Consulting, Merck Sharp & Dohme Corp., NC Registry for Brain Health, Prova Education, T3D Therapeutics, University of Southern California (USC), WebMD, from China Association for Alzheimer's Disease (CAAD) , Taipei Medical University, AD/PD Congress, Cleveland Clinic, CTAD Congress, Foundation of Learning, Health Society (Japan), INSPIRE Project; U. Toulouse, Japan Society for Dementia Research, Korean Dementia Society, National Center for Geriatrics and Gerontology (NCGG; Japan), University of Southern California (USC); owns stock-options in Alzeca, Alzheon, ALZ Path, Anven. B Vellas is an investigator in clinical trials sponsored by Biogen, Lilly, Roche, Eisai, Pfizer, Pierre Fabre Pharmaceuticals and the Toulouse University Hospital. He has served as SAB member for Biogen, Alzheon, Green Valley, Norvo Nordisk, Longeveron, Rejuvenate Biomed Clinical Pfizer, Eisai France, Advisory Board Meeting - but received no personal compensation. He has served as consultant and/or SAB member for Roche, Lilly, Eisai, TauX, Cerecin with personal compensation. S. Gauthier is a member of scientific advisory boards of Alzheon, AmyriAD, Biogen Canada, Eisai Canada, Enigma, Lily, Medesis, Roche Canada.

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How to cite this article: D. Angioni, O. Hansson, R.J. Bateman, et al. Can We Use Blood Biomarkers as Entry Criteria and for Monitoring Drug Treatment Effects in Clinical Trials? A Report from the EU/US CTAD Task Force. J Prev Alz Dis 2023;3(10):418-425; http://dx.doi.org/10.14283/jpad.2023.68