The strategic biomarker roadmap for the validation of Alzheimer's diagnostic biomarkers: methodological update

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CORRECTION

Correction to: The Strategic Biomarker Roadmap for the validation of Alzheimer's diagnostic biomarkers: methodological update

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The authors regret Table 2 needs to be rearranged so that it will be easier to be understood.

The corrected Table appears below.

This article is part of the Topical Collection on Erratum

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Table 2 Phases for the formal validation of diagnostic biomarkers according to the Strategic Biomarker Roadmap (SBR) for: case finding in oncology (3), diagnosis of Alzheimer's disease in patients with MCI (2017 adaptation from oncology (1,2)) and the 2020 update of the 2017. AD: Alzheimer's disease. MCI: mild cognitive impairment. PA: Primary Aim. SA: Secondary Aim

	Phase			Aim			Comments	
	Oncology	SBR 2017 AD (2011 criteria)	SBR 2020 AD (stage within A/T/N framework)	Oncology	SBR 2017 AD (2011 criteria)	SBR 2020 AD (stage within A/T/N framework)	SBR 2017	SBR 2020
ANALYTICAL VALIDITY (target: assay)	Phase 1			**Context of use**: **Purpose**: screening and case finding **Population**: preclinical/at risk	**Context of use**: **Purpose**: diagnosis **Population**: patients referred/-ing to clinical centers due to cognitive complaints		Diagnostic criteria for Alzheimer's disease are based on clinical features and include the use of biomarkers to increase the certainty on the etiological diagnosis of AD	Biomarker profiles combining amyloid, tauopathy and neurodegeneration lie along an AD or non-AD continuum.
	Preclinical Exploratory Studies			*PA*	To identify and prioritize leads for potentially useful biomarkers.			
	Phase 2			Phase 2 assesses Analytical Validity, i.e., the ability of the assay to detect the alteration of interest.				
	Clinical Assay Development for Clinical Disease			*PA*	To estimate the true and false positive rate or ROC curve and assess its ability to distinguish subjects with and without the disease.		*Design*: case-control. *Population*: pathological specimens from any AD stage. *Gold standard*: pathology. *Outcome*: case-control separation (sensitivity, specificity, true positive ratio, false positive ratio, and ROC curves)	*Reference standard* (clinical progression at follow-up; positivity to another AD biomarker) is allowed due to limited accessibility to pathology. However, this is a key limitation in studies of analytical validity. Thus, the use of a reference standard in Phase 2 studies should be accepted WITH WARNING.
				SA 1	To optimize procedures for performing the assay and to assess its reproducibility within/ between laboratories		The lack of reliable standard procedures to perform the essay implies that subsequent studies and diagnostic procedures include uncontrolled variability that cannot be amended post-hoc. This variability hampers the eligibility of published data for evidence-to-decision procedures.	
				SA 2	To determine the relationship between biomarker measurements made on **tumor/brain tissue** and the biomarker measurements made on the non-invasive clinical specimen		Gold standard is pathology.	*Reference standard* (clinical progression at follow-up; other biomarker) is admitted due to limited accessibility to pathology. However, this is a key limitation in studies of analytical validity accept WITH WARNING (*).
				SA 3	To assess factors (e.g. sex, age, etc.), associated with biomarker status or level in control subjects.		If such factors affect the biomarker, subpopulations need different thresholds for positivity	

Table 2 (continued)

	Phase			Aim			Comments	
				SA 4	To assess factors associated with biomarker status or level in diseased subjects—in particular, disease characteristics such as stage, histology, grade and prognosis.	To assess factors associated with biomarker status or level in cognitively impaired subjects—in particular, disease characteristics such as stage, histology, grade and prognosis.		
CLINICAL VALIDITY (target: test performance)	Phase 3				Clinical validity assesses the performance of the assay, developed in Phase-2, now used as a diagnostic test. Phase-3 studies are performed in well controlled experimental settings, examining cohorts from research centers or academic memory clinics; the biomarker is assessed, but not used to formulate the clinical diagnosis for patients. *Outcome*: case-control separation (sensitivity, specificity, true positive ratio, false positive ratio, and ROC curves)				
	Retrospective longitudinal repository studies	**Prospective longitudinal repository studies**	**Longitudinal repository studies**	*PA 1*	To evaluate, as a function of time *before clinical diagnosis*, the capacity of the biomarker to detect *preclinical disease*.	To evaluate, as a function of time *in the prodromal stage (MCI)*, the capacity of the biomarker to *predict conversion to AD dementia*	*Design*: observational prospective longitudinal case-control studies (in the absence of nested case-control longitudinal cohorts allowing retrospective examination) *Population*: MCI *Gold standard*: pathology *Reference standard*: progression to Dementia at 3 yrs (if pathology is lacking) *Outcome*: case-control separation	*Design*: in addition to the 2017 designs, cross-sectional studies, containing known risk factors for dementia (e.g., confirmed brain amyloidosis, APOE-e4, etc) are admitted as contributing construct validity evidence. Moreover, repositories may now allow *retrospective* studies also for biomarkers for the diagnosis of neurocognitive disorders *Gold standard*: clinical progression should not be considered just an acceptable reference standard in the lack of pathology, but should included in the definition of the gold standard (clinical progression + pathology). *Reference standard*: consistently with the considerations on cross-sectional design, biomarker characterization or other features can contribute to construct validity. However, clinical progression generates stronger evidence than other reference standards based on construct validity. *Outcome*: case-control separation (sensitivity, specificity, true positive ratio, false positive ratio, and ROC curves)
				PA 2	To define criteria for a positive **screening** test in preparation for Phase-4	Define criteria for a positive **diagnostic** test for MCI due to AD, in preparation of Phase-4	"in preparation of Phase-4": in phase 3, the biomarker is assessed in strictly experimental conditions. Patients are tested, but their diagnosis is NOT based on the biomarker under examination. Here, the biomarker's features are adjusted to allow its use for clinical diagnosis in Phase 4.	

Table 2 (continued)

Phase	Aim			Comments
	SA 1	To explore the impact of covariates on the discriminatory abilities of the biomarker before clinical diagnosis		Note the difference between Phase-3_SA1 and Phase-2_SA3-4: in Phase 2, covariates are assessed relative to their effect on status or level of the biomarker, and on the threshold for positivity, in order to define *the assay*. In Phase 3, covariates are explored relative to their effect on the discriminatory ability of the biomarker, i.e., in using the *assay as a test*.
	SA 2	To compare markers to select the most promising		SA2: Compare markers: study design must quantify not only the diagnostic accuracy of the target biomarker (index test), but also the accuracy of the traditional or alternative procedure, in order to quantify the *incremental* diagnostic value of the target biomarker. The compared *outcomes are* case-control separation (sensitivity, specificity, true positive ratio, false positive ratio, and ROC curves)
	SA 3	To develop algorithms for **screening** based on combinations of markers.	Develop algorithms for the biomarker-based **diagnosis** of MCI in preparation of Phase-4.	Phase-3_SA2-3 provide the data to combine markers and define diagnostic algorithms guiding clinicians' use of biomarkers in Phase-4. *Outcome*: case-control separation (sensitivity, specificity, true positive ratio, false positive ratio, and ROC curves) obtained with combinations of biomarkers
	SA 4	To determine a **screening** interval for phase 4 if repeated testing is of interest.	To determine an interval able to detect a meaningful change of **biomarker** status or level in progressing MCI	
Phase 4	In Phase-4, the biomarker, still under investigation, is used also in non-academic clinical contexts to support patient diagnosis. The experimental use of the biomarker should be made explicit to patients. Phase-4 provides validation data on the use of the biomarker in real-world rather than strictly controlled conditions. Sample sizes are larger than in Phase-3.			

Table 2 (continued)

Phase		Aim			Comments	
Prospective Screening Studies	**Prospective Diagnostic Studies**	*PA*	To determine the operating characteristics of the biomarker-based **screening** test in a relevant population by determining the detection rate and the false referral rate.	To determine the operating characteristics of the biomarker-based **diagnostic** test in MCI patients in the memory clinics population	*Design*: prospective longitudinal studies (Studies at this stage involve testing people and lead to diagnosis and treatment). *Population*: same as Phase-3 (size: hundreds, from tertiary referral centres). *Gold/reference standard*: like Phase-3 *Outcome*: proportion of cases correctly diagnosed; baseline correlates of biomarker positivity (age, severity, etc); compliance with the programme; disease-associated morbidity, quality of life, costs	Design, Population, Gold standard: same as Phase 3. Outcome: same as 2017
		SA 1	To describe the characteristics of **tumors** detected by the **screening** test—in particular, with regard to the potential benefit incurred by early detection.	To describe the characteristics of **the neurodegenerative disorder** detected by the **diagnostic** biomarker—in particular, with regard to the potential benefit incurred by early detection.		
		SA 2	To assess the practical feasibility of implementing the **screening** program and compliance of test-positive subjects with work-up and treatment recommendations	To assess the practical feasibility of implementing the **biomarker-based diagnostic** procedure and compliance of test-positive subjects with work-up recommendations.		The emotional and social implications related to positive test results within the diagnostic procedure may need to be assessed and taken into account, to increase compliance to work-up recommendations. This was done in oncology, also based on a counselling and patient involvement that is not yet fully developed in the field of dementia

Table 2 (continued)

	Phase		Aim			Comments
			SA 3	To make preliminary assessments of the effects of **screening** on costs and mortality associated with **cancer**.	To make preliminary assessments of the effects of **biomarker-based diagnosis** on costs and burden associated with AD	Outcome definition is still insufficient to cover this aim properly (30) and should be solved with priority.
			SA 4	To monitor **tumors** occurring clinically but not detected by the **screening** protocol	To monitor **AD dementia/ neurocognitive disorders** occurring clinically but not detected by the **biomarker-based diagnostic** procedure	
CLINICAL UTILITY	**Phase 5**			Phase-5 entails surveillance studies on thousands of subjects.		
	Cancer Control Studies	**Disease Control Studies**	*PA*	To estimate the reductions in **cancer** mortality **afforded by the screening test**	To estimate the effects of biomarker-based diagnosis on **disease-associated** mortality, **morbidity, and disability.**	Design: surveillance system of accepted practice *Population*: = same as Phase-4 (size: thousands, from secondary referral centres) *Outcome*: proportion of cases correctly diagnosed; baseline correlates of biomarker positivity (age, severity, etc); compliance with the programme; disease-associated morbidity, quality of life, costs
			SA 1	To obtain information about the costs of **screening** and treatment and the cost per life saved.	To obtain information about the costs of **biomarker-based diagnosis** per **quality-adjusted years of life**.	
			SA2	To evaluate compliance with **screening** and work-up in a diverse range of settings.	To evaluate compliance with **biomarker-based diagnostic** work-up in a diverse range of settings.	
			SA 3	To compare different **screening** protocols and/or to compare different approaches to treating **screen-detected** subjects in regard to effects on mortality and costs.	To compare different **biomarker-based diagnostic** protocols and/or to compare different approaches to treating **biomarker-based diagnosed** subjects in regard to effects on **quality-adjusted years of life,** mortality and costs.	