IC-P-003 OPTIMAL REFERENCE REGION TO MEASURE LONGITUDINAL AMYLOID-BETA CHANGE WITH 18F-FLORBETABEN PET

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Background: Accurate measurement of amyloid-beta (Aβ) change is important in anti-Aβ therapeutic trials. Selecting the optimal reference region (RR) is essential to reduce the variance of the Aβ burden PET measurements, allowing early detection of treatment efficacy. The study objective was to determine the RR that allows earlier detection of subtle Aβ changes using 18F-florbetaben (FBB) PET. **Methods:** FBB PET scans from 45 mild cognitively impaired (MCI) patients (72.69 ± 6.54 yrs., 29 male/16 female) who underwent three FBB scans were included (baseline (n=45), one-year (n=41) and two-years (n=36)). FBB scans were visually assessed as positive and negative. Cortical regions (frontal, lateral temporal, occipital, parietal, anterior cingulate and posterior cingulate) were quantified using the standardized AAL region-of-interest (ROI) atlas applied to the spatially normalized gray matter PET image obtained from the segmentation of the participant's baseline T1-weighted volumetric MRI. Four regions of reference (gray matter cerebellum (CGM), whole cerebellum (WCER), pons (PONS) and subcortical white matter (WM)) were studied. Cortical standardized uptake value ratio (SUVR) for each RR was calculated dividing cortex activity by the RR activity. A composite SUVR averaged all cortical regions. T-test was used to compare SUVR at baseline to the SUVR from one- and two-years follow-up scans. **Results:** Both CGM and WCER RRs enabled early detection of cortical SUVR changes that were in concordance with the anticipated pattern of change for the MCI patients. Average percent of Aβ accumulation per year (mean±SD) derived from composite SUVR in negative (-) and positive (+) scans was 0.13±1.68(-)/1.39±2.02(+) for CGM, 0.16 ± 1.43(-)/1.36±1.79(+) for the WCER. Composite SUVR increase in positive scans was significantly larger than those in negative scans between baseline and 1-year follow-up (p(CGM)=0.04, p(WCER)=0.02) and between baseline and 2-years follow-up scans (p(CGM)=0.04, p(WCER)=0.02). PONS detected significant changes only at 2-years follow-up (p(1-yr)=0.71, p(2-yrs)=0.001) while SWM did not show significant difference either follow-up (p(1-yr)=0.50, p(2-yrs)=0.04). **Conclusions:** Reference region selection influences the reliable and early measurement of amyloid-beta changes. Compared with WM or PONS, cerebellar reference regions (CGM and WCER) are recommended as RR for 18F-florbetaben PET since they allow earlier detection of amyloid-beta change.

IC-P-004 THE BIOMARKER-BASED DIAGNOSIS OF ALZHEIMER'S DISEASE: LESSONS FROM ONCOLOGY

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Phases for the development of biomarkers as adapted from the oncology framework (Pepe et al., J Natl Cancer Inst 2001) to the case of the pre-dementia diagnosis of Alzheimer's disease.

PHASES	AIMS	description
Phase 1		
Pilot Studies	Primary Aims	To identify leads for potentially useful biomarkers and prioritize identified leads.
Phase 2		
Clinical Assay	Primary Aim	To estimate the true and false positive rate or ROC curve and assess its ability to distinguish subjects with and without the disease.
Development for Clinical Disease		
	Secondary Aim 1	To optimize procedures for performing the assay and to assess the reproducibility of the assay within and between laboratories.
	Secondary Aim 2	To determine the relationship between biomarker tissue measurements made on tissue (phase 1) and the biomarker measurements made on the noninvasive clinical specimen (phase 2).
	Secondary Aim 3	To assess factors (e.g. sex, age, etc.), associated with biomarker status or level in control subjects. If such factors affect the biomarker, thresholds for test positivity may need to be defined separately for target subpopulations.
	Secondary Aim 4	To assess factors associated with biomarker status or level in diseased subjects—in particular, disease characteristics.
Phase 3		
Prospective Longitudinal	Primary Aim 1	To evaluate the capacity of the biomarker to detect the earliest disease stages.
Repository Studies	Primary Aim 2	To define criteria for a biomarker positive test in preparation for phase 4.
	Secondary Aim 1	To explore the impact of covariates on the discriminatory abilities of the biomarker before clinical diagnosis.
	Secondary Aim 2	To compare markers with a view to selecting those that are most promising.
	Secondary Aim 3	To develop algorithms for positivity based on combinations of markers.
	Secondary Aim 4	To determine a biomarker testing interval for phase 4 if repeated testing is of interest.
Phase 4		
Prospective Diagnostic Studies	Primary Aim	To determine the operating characteristics of the biomarker-based test in a relevant population by determining the detection rate and the false referral rate. Studies at this stage involve testing people and lead to diagnosis and treatment.
	Secondary Aim 1	To describe the characteristics of disease detected by the biomarker test—in particular, with regard to the potential benefit incurred by early detection.

(*Continued*)

Phases for the development of biomarkers as adapted from the oncology framework (Pepe et al., J Natl Cancer Inst 2001) to the case of the pre-dementia diagnosis of Alzheimer's disease. (*Continued*)

PHASES	AIMS	description
	Secondary Aim 2	To assess the practical feasibility of implementing the diagnostic program and compliance of test-positive subjects with work-up and treatment recommendations.
	Secondary Aim 3	To make preliminary assessments of the effects of biomarker testing on costs and mortality associated with the disease.
	Secondary Aim 4	To monitor disease occurring clinically but not detected by the biomarker testing protocol.
Phase 5		
Disease Control Studies	Primary Aim	To estimate the reductions in disease-associated mortality, morbidity. and disability afforded by biomarker testing.
	Secondary Aim 1	To obtain information about the costs of biomarker testing and treatment and the cost per life saved or per quality-adjusted life year.
	Secondary Aim 2	To evaluate compliance with testing and work-up in a diverse range of settings.
	Secondary Aim 3	To compare different biomarker testing protocols and/or to compare different approaches to treating test positive subjects in regard to effects on mortality and costs.

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Background: The use biomarkers for Alzheimer's disease (AD) in clinical settings is regulated relatively loosely compared, for example, to requirements for introducing new drugs. In 2001, the framework used for drugs validation was adapted to design a strict and systematic validation procedure for oncology biomarkers. This work aims to adapt the oncology framework to AD specific biomarkers. **Methods:** The 5-phases framework by Pepe et al (Journal of the National Cancer Institute, 93(14), 2001) was adapted to meet the specificity of validation studies of biomarker for AD. Adaptations were made to: specific terms; types of studies design; context of use; target population. Limitations of these adaptations were thoroughly considered. **Results:** The adaptation led to Incidental and Substantial differences of the 'AD', compared to the 'oncology', framework. Incidental differences relate to target tissue (brain vs tumor), specific outcomes (disability, morbidity, institutionalization, quality of life, caregivers burden vs mortality), and study designs (prospective vs retrospective). Substantial differences relate to the target population and to the possible use of biomarkers within the two frameworks. As to target population, this validation framework is restricted to the MCI population, due to the need of early detection of clinical disease, to the fact that clinical criteria do not recommend preclinical diagnosis for ethical reasons, and to the possibility to use 'conversion to dementia' as a gold standard for diagnosis (in the lack of pathology data). The resulting 5 sequential phases were: 1) pilot studies, 2) clinical assay development for clinical disease, 3) prospective longitudinal repository studies, 4) prospective diagnostic studies, and 5) disease control studies (Table). Because of the required adaptations, biomarkers for AD can be used for biomarker-based diagnoses and not yet for screening purposes. **Conclusions:** The adaptation of the oncology framework to AD aims to systematize the validation of AD biomarkers. The important limitations restrict the generalizability of results to the general population and the use of such biomarkers for screening purposes. This initiative should be considered as a first, although necessary, step to the definition of a systematic validation of biomarkers for AD.

IC-P-005 DOES CLINICAL USE OF AMYLOID-PET AFFECT PHYSICIANS' BELIEFS ON THE PATHOGENETIC ROLE OF AMYLOID-β AND THE CLINICAL USAGE OF AMYLOID-PET?

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Background: Previous data suggest that beliefs on the pathogenic role of amyloid-beta in AD do not affect the intended clinical use of amyloid-PET (Boccardi et al., 2016). Here, we evaluate whether practice in clinical use of amyloid-PET, in turn, affects physicians' beliefs on the role of amyloid-B (AB) in AD and the intended clinical usage of amyloid-PET. **Methods:** We administered a questionnaire at the beginning, in the middle and at the end of a study using amyloid-PET. Physicians indicated their belief regarding the role of AB in the AD pathogenesis ('belief'), and then expressed the probability of diagnostic change after amyloid-PET in three hypothetical scenarios: 'AD-negative', 'NonAD-positive' and 'NonAD-negative'. Differences in the probability of diagnostic change between scenarios and over time were evaluated through a linear mixed model with 'belief'