

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 (A β) change is important in anti-A β therapeutic trials. Selecting the optimal reference region (RR) is essential to reduce the variance of the A β burden PET measurements, allowing early detection of treatment efficacy. The study objective was to determine the RR that allows earlier detection of subtle A β changes using 18F-florbetaben (FBB) PET. **Methods:** FBB PET scans from 45 mild cognitively impaired (MCI) patients (72.69 \pm 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 A β accumulation per year (mean \pm SD) derived from composite SUVR in negative (-) and positive (+) scans was 0.13 \pm 1.68(-)/1.39 \pm 2.02(+) for CGM, 0.16 \pm 1.43(-)/1.36 \pm 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.

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