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'

Table
Changes in the diagnostic confidence between scenarios and over the time.

	T00	T06	T12	T06-T00		T12-T06		T12-T00	
Variables	mean (SD)	mean (SD)	mean (SD)	mean_diff (SD_diff)	Cohen's *d*	mean_diff (SD_diff)	Cohen's *d*	mean_diff (SD_diff)	Cohen's *d*
Befief (0-10)	5.86 (1.47)	6.29 (1.59)	7.00 (2.02)	0.43 (1.35)	*0.32*	0.71 (1.60)	*0.45*	1.14 (1.87)	*0.61*
Scenario 1 (0-100%)	54.29 (31.55)	66.21 (31.85)	55.50 (30.30)	11.93 (31.57)	*0.38*	-10.71 (26.84)	**-0.40**	1.21 (38.72)	0.03
Scenario 2 (0-100%)	67.14 (25.17)	55.00 (30.57)	71.07 (29.96)	-12.14 (26.10)	**-0.46**	16.07 (32.74)	*0.49*	3.93 (11.45)	*0.34*
Scenario 3 (0-100%)	23.33 (26.71)	20.48 (23.34)	18.09 (18.06)	-2.86 (33.66)	-0.08	-2.38 (25.19)	-0.09	-5.24 (24.06)	**-0.22**

Values for the three scenarios refer to percentages. Cohen's *d* is an index of effect size: defined as the difference between two means divided by a standard deviation for the data. Mean_diff is the difference between two time points, SD_diff is calculated with the following formula: SD_pre*sqrt(2*(1-rho)), where rho is the correlation coefficient. Values are in italics or bold when the Cohen's *d* is at least 'small' ($\geq$ 0.20): italics for positive difference and bold for negative.

as covariate. Effect Size indices (ES; Cohen's *d* for repeated measures) were also computed. We analyzed the seven dementia experts who both filled out the questionnaire at all time points and enrolled a minimum of 15 patients. **Results:** 'Belief' did not affect the probability of diagnostic change in different scenarios and over time (p=0.655). The probability of diagnostic change did not change significantly throughout the study for all scenarios (p=0.970). Due to the very small sample size, we considered ES greater than 0.20 ('small'). These were consistent with: i) a trend in increase in the belief on a causal role of AB in AD and ii) a growth of the positive predictive value of the amyloid-PET in 'NonAD-positive' over the whole study (Table). **Conclusions:** Beliefs on the pathogenic role of amyloid-B do not affect the intended clinical use of amyloid-PET in the course of a naturalistic study using amyloid-PET. ES suggested an increase of the belief in a causal role of AB in AD pathogenesis over the study. Moreover, an increased use of the positive predictive value of amyloid-PET emerged after practical usage of amyloid-PET. These results will be compared with the actual use of amyloid-PET by the same physicians.

IC-P-006 REGIONAL BETA-AMYLOID PET COMPARISON ACROSS ATYPICAL AND TYPICAL VARIANTS OF ALZHEIMER'S DISEASE

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Background: Typical dementia of the Alzheimer's type (DAT) presents as a primary amnestic syndrome, and three "atypical" variants are now recognized. Two of these atypical variants include posterior cortical atrophy (PCA), which presents with visual deficits and the logopenic variant of primary progressive aphasia (lvPPA), which presents with primary language disruption, both of which are commonly due to Alzheimer's disease pathology. Here, we compare these Alzheimer's disease variants on the pattern of beta-amyloid deposition on PiB PET, as well as cognitive measures. **Methods:** We matched 27 PCA, 50 LPA, and 77 DAT patients on age, gender, and disease duration as best as possible. Only subjects with positive beta-amyloid deposition on PiB PET, defined using a standardized uptake value ratio (SUVR) of $\geq$ 1.5, were included. All voxels in the PiB-PET images were divided by median uptake in cerebellum and transformed into template space. Partial volume correction (PVC) was performed. Voxel-level comparisons were performed across groups both with and without PVC using SPM5. **Results:** were assessed after correction for multiple comparisons using family-wise error at p<0.05.Subjects also completed memory, language, and visuospatial tests that may have been used to augment DAT and PCA diagnosis, but was not used in diagnosis of LPA. Results: Cognitively, DAT subjects had poorer memory than lvPPA and PCA subjects, lvPPA subjects had poorer language scores than DAT and PCA subjects, and PCA had poorer visuospatial scores that lvPPA and DAT subjects. The groups did not differ on global SUVR. Regional distribution of PiB-PET was similarly widespread in each of the three groups, although PCA showed greater uptake in bilateral occipital lobe compared to DAT, and greater uptake in right occipital lobe compared to lvPPA. These findings were observed both with and without PVC. No other regional PiB-PET differences were observed across groups. **Conclusions:** These findings suggest that while beta-amyloid deposition is typically diffuse in Alzheimer's disease variants, regional differences exist as compared to DAT, although this DAT group may represent those with an earlier onset. The occipital lobe is particularly vulnerable to beta-amyloid deposition, as well as neurodegeneration, in PCA.

IC-P-007 BRAIN AMYLOIDOSIS AND COGNITIVE DECLINE IN MCI: 12-MONTH FOLLOW-UP

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Background: Two previous studies demonstrated greater cognitive decline in MCI patients with positive amyloid-PET compared to negative MCI, as assessed by several neuropsychological tests, over 18 (Doraiswamy et al., 2012) and 36 months (Doraiswamy et al., 2014) follow-up. Our aim is to evaluate whether positive amyloid-PET scans are predictive of greater cognitive decline than negative scans over a shorter 12 months period. **Methods:** A naturalistic series of seventy-six MCI patients underwent amyloid-PET with ^{18}F-Florbetapir (FBP-PET), and homogeneous clinical and neuropsychological multi-domain assessment before FBP-PET and after 12 months (12-FU). For each neuropsychological test we constructed a linear mixed model with scores as the dependent variable, and 'FBP-PET result' (positive or negative) and 'time' (baseline or 12-FU) as main factors. 'Age' and 'education' were included as covariates. Effect size indices (partial Eta-squared, η_p^2) were also computed (0.02, 0.13 and 0.26 referring respectively to small, medium and large Eta-squared). **Results:**