Synopsis of a tentative translation of Alzheimer's biomarkers to Sullivan Pepe and colleagues's framework (Sullivan Pepe et al., J Natl Cancer Inst 2001).		
	General statement	**Evidence in Alzheimer's disease**
Phase 1— Preclinical Exploratory Studies	*Primary Aims:* To identify leads for potentially useful biomarkers and prioritize identified leads.	Neurobiological studies showing that: plaques contain A· 42; neurofibrillary tangles contain hyperphosphorilated tau; neuronal loss in the hippocampus; and glucose being the primary metabolic substrate of synaptic function.
Phase 2— Clinical Assay Development for Clinical Disease	*Primary Aim*: to estimate the true and false positive rate or ROC curve and assess ability to distinguish subjects with and without the disease.	Case-control studies showing that AD biomarkers separate AD dementia patients from older healthy volunteers. Few have used the ideal standard of truth of pathological diagnosis of AD.
	Secondary Aims 1) To optimize procedures for performing the assay and to assess the reproducibility of the assay within and between laboratories.	Development of SOPs for AD biomarker collection and measurement, e.g. ADNI sequences for high-resolution volumetric MR, EADC-ADNI harmonized protocol for manual hippocampal segmentation, procedures for signal acquisition and interpretation of fluorinated PET amyloid ligands.
	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).	Correlation between: hippocampal volume on MR *in vivo* and neurodegenerative changes on pathology; uptake of fluorinated PET amyloid ligands *in vivo* and senile plaque density on pathology; and glucose consumption in association cortex *in vivo* and neurodegenerative changes on pathology.
	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.	Correlation between hippocampal and intracranial volume in healthy persons.
	4) To assess factors associated with biomarker status or level in diseased subjects—in particular, disease characteristics.	Effect size of most core biomarkers varies by age at onset.
Phase 3— Retrospective Longitudinal	*Primary Aims:* to evaluate the capacity of the biomarker to detect the earliest disease stages and define criteria for a biomarker positive test in preparation for phase 4.	Predictivity of incident AD dementia in MCI patients and healthy older volunteers by individual biomarkers and combinations.

Repository Studies	*Secondary Aims* 1) To explore the impact of covariates on the discriminatory abilities of the biomarker before clinical diagnosis.	Preliminary evidence on association of age at onset with predictivity of core biomarkers.
	2) To compare markers with a view to selecting those that are most promising.	Preliminary evidence on association of two or more core biomarkers.
	3) To develop algorithms for positivity based on combinations of markers.	Preliminary evidence on association of CSF Aβ42, FDG-PET, and hippocampal atrophy.
	4) To determine a biomarker testing interval for phase 4 if repeated testing is of interest.	Not assessed.
Phase 4—Prospective Case Finding Studies	*Primary Aim: t*o 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.	Not assessed.
	Secondary Aims 1) To describe the characteristics of disease detected by the biomarker test—in particular, with regard to the potential benefit incurred by early detection.	Not assessed.
	2) To assess the practical feasibility of implementing the case finding program and compliance of test-positive subjects with work-up and treatment recommendations.	Not assessed.
	3) To make preliminary assessments of the effects of biomarker testing on costs and mortality associated with the disease.	Association of fluorinated PET amyloid ligands with lower use of health care resources.
	4) To monitor disease occurring clinically but not detected by the biomarker testing protocol.	Not assessed.
Phase 5—Disease Control Studies	*Primary Aim:* to estimate the reductions in disease-associated mortality, morbidity, and disability afforded by biomarker testing.	Not assessed.
	Secondary Aims 1) To obtain information about the costs of biomarker testing and treatment and the cost per life saved or per quality-adjusted life year.	Not assessed.
	2) To evaluate compliance with testing and work-up in a diverse range of settings.	Not assessed.
	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.	Not assessed.