Title: Clinical validity of increased cortical uptake of amyloid ligands on PET as a biomarker for Alzheimer's disease in the context of a structured 5-phase development framework

Authors: Konstantinos Chiotis¹, Laure Saint-Aubert¹, Marina Boccardi^{2,3}, Anton Gietl⁴, Agnese Picco⁵, Andrea Varrone⁶, Valentina Garibotto⁷, Karl Herholz⁸, Flavio Nobili⁵, Agneta Nordberg^{1,9}, and the Geneva Task Force for the Roadmap of Alzheimer's Biomarkers*

Affiliations: ¹Dept NVS, Center for Alzheimer Research, Translational Alzheimer Neurobiology, Karolinska Institutet, Stockholm, Sweden; ²LENITEM (Laboratory of Epidemiology, Neuroimaging and Telemedicine), IRCCS S.Giovanni di Dio Fatebenefratelli, Brescia, Italy; ³LANVIE – Laboratory of Neuroimaging of Aging, University of Geneva, Switzerland; ⁴Division of Psychiatry Research and Psychogeriatric Medicine, University of Zurich, Zurich, Switzerland; ⁵Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Largo Daneo 3, 16132 Genoa, Italy; ⁶Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet, Stockholm, Sweden; ⁷Department of Neurology, Geneva University Hospitals, 4, rue Gabrielle Perret-Gentil, 1205, Geneva, Switzerland; ⁸The University of Manchester, Institute of Brain, Behaviour and Mental Health, Wolfson Molecular Imaging Centre, 27 Palatine Road, Manchester, M20 3LJ, UK; ⁹Department of Geriatric Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden.

*A complete listing of the Geneva Task Force for the Roadmap of Alzheimer's Biomarkers investigators can be found at [http://centroalzheimer.it/public/MB/BM-Roadmap/The Geneva AD Biomarker Roadmap Task Force.docx](http://centroalzheimer.it/public/MB/BM-Roadmap/The%20Geneva%20AD%20Biomarker%20Roadmap%20Task%20Force.docx)

Corresponding author: Agneta Nordberg, MD, PhD, professor
Karolinska Institutet, Dept NVS, Center for Alzheimer Research
Division of Translational Alzheimer Neurobiology, Novum 5th floor
141 57 Huddinge, Sweden
Mail: Agneta.K.Nordberg@ki.se
Phone: +46 8 585 854 67; Fax: +46 8 585 854 70

Abstract

The use of biomarkers has been proposed for diagnosing Alzheimer's disease (AD) in recent criteria, but some biomarkers have not been sufficiently investigated to justify their routine clinical use. Here we evaluate in a literature review the clinical validity of amyloid PET imaging using a structured framework developed for the assessment of oncological biomarkers. Homogenous criteria have been addressed in reviews of other AD biomarkers. There is adequate evidence that the main aims of phases 1 (rationale for use) and 2 (discriminative ability) have been achieved. The aims of phase 3 (early detection ability) have been partly achieved, while phase 4 studies (performance in representative mild cognitive impairment patients) are currently on-going. Phase 5 studies (quantification of impact and costs) are still to come. This review highlights the priorities to be pursued to enable the proper use of amyloid PET imaging in a clinical setting. Future investigations will primarily be large, phase 4 studies that will assess the utility of amyloid PET imaging in routine clinical practice.

Graphical abstract:

Development of **amyloid PET** adapted from the framework of Pepe et al. 2001

Phase 1: Rationale for the use of amyloid PET		Phase 2: Discrimination ability of amyloid PET		Phase 3: Detection ability in early phase		Phase 4: Amyloid PET accuracy in representative MCI patients		Phase 5: Impact of amyloid PET-based diagnosis on relevant outcomes	
Primary aim	Primary aim	Secondary aims	Primary aims	Secondary aims	Primary aim	Secondary aims	Primary aim	Secondary aims	
Potential leads	Identify discrimination accuracy AD/HC	Assay definition	Assess capacity of earliest (MCI) detection	Impact of covariates	Assess true/false referral rate in amyloid PET diagnosed patients	Detect predictive features	Estimate impact on morbidity & disability	Cost/benefit quantification	
		Ante mortem/autopsy		Compare markers		Practical feasibility		Compliance in different settings	
		Covariates in HC		Combine markers		Estimate impact & costs		Compare different protocols	
									Covariates in AD
Achievement			Criteria for positivity						
Full	Partial								
Preliminary	Not achieved								

Keywords: Amyloid; Alzheimer's disease; biomarker; positron emission tomography; development; neuroimaging; early diagnosis; biomarker-based diagnosis; clinical validity; 5-phases

Abbreviations: A β : amyloid beta; AD: Alzheimer's disease; ApoE4: apolipoprotein E ϵ 4; CSF: cerebrospinal fluid; FDA: US Food and Drug Administration; EMA: European Medicines Agency; HCs: healthy controls; MCI: mild cognitive impairment; MRI: magnetic resonance imaging; PET: positron emission tomography; PIB: Pittsburgh compound b; ROC: receiving operator characteristic.

1. Introduction

In order to establish an accurate, early diagnosis for Alzheimer's disease (AD), two different sets of recently proposed criteria have suggested the use of biomarkers as part of the clinical assessment of patients with cognitive complaints (Albert, et al., 2011, Dubois, et al., 2014, Morris, et al., 2014). However, several of these biomarkers have only recently been discovered and investigation of the accuracy and applicability of the available biomarkers is thus at varying stages. One of the greatest challenges is to assess their usefulness in the face of this heterogeneity and address any critical issues before their widespread implementation into clinical routine.

In contrast to the drug pipeline development process, biomarker development does not follow a linear process. To overcome a similar problem in the field of oncology, Pepe, et al. (2001) suggested that the investigation of cancer biomarkers should be systematised according to a five-phase framework derived from the drug development process. A similar approach applied to the field of dementia could strengthen the adoption of biomarkers for AD diagnosis in clinical practice.

This review covers only part of this wider plan, i.e. the analysis of the progress in the investigative process for amyloid positron emission tomography (PET) imaging for AD diagnosis at an early symptomatic stage, using the oncology framework. Other studies from this effort assessed, in the common framework, the following biomarkers: episodic memory assessment (Cerami, et al., in this issue), cerebrospinal fluid (CSF) measures (Mattsson, et al., in this issue), medial temporal atrophy (Ten Kate, et al., in this issue), [^{18}F]FDG PET (Garibotto, et al., in this issue), [^{123}I]-loflupane imaging and [^{123}I]-MIBG imaging (Sonni, et al., in this issue).

The recent development of amyloid-specific PET ligands has enabled *in vivo* visualisation of fibrillar amyloid-beta (A β) plaques. Since the emergence of [^{11}C]Pittsburgh compound B ([^{11}C]PIB), the first and most widely studied amyloid-specific ligand (Klunk, et al., 2004), the field of

amyloid PET imaging has vastly expanded. The short half-life of [^{11}C] has limited its use to centres with direct access to cyclotron facilities, which led to the development of [^{18}F] derivatives (Mathis, et al., 2012). The longer half-life of [^{18}F] enabled the ligands to be delivered to geographically dispersed sites, thus enabling the clinical use of amyloid PET imaging. Three [^{18}F] amyloid-specific PET ligands have already received approval from both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for excluding the presence of A β pathology in individuals with cognitive decline. These [^{18}F] ligands are florbetapir (AV-45, AmyvidTM), flutemetamol (GE067, VizamyTM), and florbetaben (AV-1, BAY94-9172, NeuraceqTM). Although not yet approved, other promising ligands, such as [^{18}F]AZD4694 (NAV4694), have been developed (Rowe, et al., 2013b).

This review systematically investigates the advances in amyloid PET imaging using data from studies of these [^{18}F] ligands or [^{11}C]PIB. Evidence was interpreted in the light of the oncology framework (Pepe, et al., 2001) adapted to the AD field (Boccardi, et al., in this issue, Frisoni, et al., in this issue), in order to define the clinical validity of amyloid PET imaging for the diagnosis of AD in the pre-dementia stage.

2. Methods

2.1 Target

This review was performed with the specific aim of improving the differential diagnosis of AD at the prodromal stage (Boccardi, et al., in this issue, Frisoni, et al., in this issue).

The target population comprised subjects with mild cognitive impairment (MCI), as defined in section 2.2. Only patients with sporadic (not autosomal dominant) AD were considered. The standard reference for the diagnosis was AD neuropathology or development of incidental AD dementia (as defined in section 2.2) after 2 years of follow-up. For the purposes of this review, only [^{11}C]PIB (due to its wide use in research) and the three approved [^{18}F] ligands (florbetapir, flutemetamol, and florbetaben) were considered as amyloid-specific PET ligands. The available evidence for the ligand [^{18}F]FDDNP was not reviewed in the present work since the ligand shows affinity for both A β and neurofibrillary tangle pathologies (Agdeppa, et al., 2001, Shoghi-Jadid, et al., 2002, Small, et al., 2006, Smid, et al., 2006).

2.2 Glossary

The lexicon of this framework has been extensively described in Frisoni, et al. (in this issue), and is summarised here.

Alzheimer's disease (AD). The term AD is used here to mean Alzheimer's pathology consisting of cerebral A β plaques and tangles, supposedly leading to pattern-specific neurodegeneration (medio-temporal and temporo-parietal). The term is thus independent of the clinical manifestation of the disease.

AD dementia. This term encompasses the clinical syndrome featuring the acquired, progressive cognitive impairment associated with functional disability as defined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (McKhann, et al., 1984). Notably, not all cases of clinically diagnosed AD dementia have AD pathology because of the imperfect accuracy of purely clinical criteria.

Mild cognitive impairment (MCI). The term MCI indicates acquired objective cognitive impairment but normal activities of daily living, and is applied to patients likely to progress to AD dementia (about 50%), patients with no neurodegenerative disorder (about 35-40%) and those with non-AD neurodegeneration (about 10-15%) (Bennett, et al., 2002, Jack, et al., 2008, Rowe, et al., 2010).

Non-AD neurodegenerative disease. The included neurodegenerative disorders that fall outside the AD sphere belong to a large pathological spectrum that includes hippocampal sclerosis, frontotemporal lobar degeneration, progressive supranuclear palsy, corticobasal degeneration, Lewy body dementia and other alpha-synucleinopathies such as multiple system atrophy, and any suspected non-amyloid-related pathology.

2.3 Conceptual framework

The main phases of the present framework used to describe the development of the biomarkers resemble the phases used in the oncological framework. The shift of the reference methodological model from the field of oncology to that of dementia implies a shift of aims from screening to diagnosis, as the examined biomarkers are validated for use in the clinical population already diagnosed with MCI.

Here we summarize the resulting points of this translation, addressing the steps to fulfil for the systematic development of biomarkers for diagnosing dementia as a clinical routine.

Phase 1. This phase consists of preclinical exploratory studies with the primary aim of identifying the rationale of the biomarker, based on pathology findings.

Phase 2. This phase consists of studies investigating the ability of the biomarker to discriminate between patients and healthy controls (HCs). The studies focus on defining the clinical assays that allow reliable discrimination, with assessment of the possible differential effects of factors in patients and HCs that could influence the thresholds of positivity. The relevant factors for amyloid imaging were age, gender, apolipoprotein E ϵ 4 (ApoE4) allele carrier status and educational attainment.

Phase 3. This phase consists of studies aiming to define the ability of the biomarker to detect the disease in its early phase, i.e. the prodromal stage for this review. These are prospective, longitudinal, repository studies that fine-tune the exact threshold for positivity, and compare the usefulness of the biomarker, either alone or in combination, with that of other available biomarkers.

Phase 4. This phase consists of studies aiming to estimate the accuracy and usefulness of the biomarker-based diagnosis in representative MCI patients. These are prospective, diagnostic studies in subjects undergoing drug treatment following the biomarker-based diagnosis. They assess the beneficial effect of the biomarker-based detection in terms of early diagnosis, feasibility, and compliance, and provide preliminary evidence about mortality, costs, and undetected cases.

Phase 5. This phase consists of studies aiming to exactly quantify the impact of the biomarker-based diagnosis on clinically meaningful outcomes and costs. These are disease-control studies, which assess the reduction in mortality, morbidity, disability and costs associated with the biomarker-based diagnosis. They also aim to compare the costs of different biomarker testing protocols and settings.

This review assesses the clinical validity of amyloid PET imaging with respect to each of these five phases. Detailed primary and secondary aims were defined for each phase, as described in Table 1 and section 3.

2.4 Evidence evaluation

For all phases, the literature was searched in order to evaluate whether each aim was Fully Achieved, was Partly Achieved, had Preliminary Evidence of achievement, or was Not Achieved, as defined below.

Fully Achieved: scientific evidence was available and replicated in consecutive adequately powered studies without major methodological faults.

Partly Achieved: scientific evidence was available but not yet sufficiently replicated, studies were not adequately powered, other significant methodological limitations were found, or specific aspects of each aim were not sufficiently addressed.

Preliminary evidence: only evidence from case series or abstract presentations was available.

Not Achieved: no evidence was available from published or on-going studies at the time of writing this review.

2.5 Paper search and selection

For each phase, the literature was searched for evidence of achieving the above aims. PubMed database was searched for relevant studies. Specific search strings were used to circumscribe the search to the relevant aims (see supplementary table S1 at http://centroalzheimer.it/public/MB/BM-Roadmap/BiomarkerRoadmap_Suppl.docx). The original keywords used to identify papers about amyloid PET imaging were: ("Positron Emission Tomography" OR "PET") AND ("PIB" OR "Pittsburgh compound b" OR "Pittsburgh compound-b" OR "Florbetapir" OR "AV45" OR "AV-45" OR "Amyvid" OR "Flutemetamol" OR "Vizamyl" OR "GE067" OR "Florbetaben" OR "av-1" OR "BAY94-9172" OR "Neuraceq"). In order to assess phase 2 studies the following keywords were added to the original ones mentioned above: ("controls" OR "normal") AND ("Alzheimer*"). For phase 3 studies the following keywords were added to the original keywords: ("MCI" OR "Mild cognitive Impairment") AND ("follow-up" OR "conversion" OR "progression" OR "prediction"). When aims were widely achieved, the authors selected a reference paper, a review or a meta-analysis. In case of lacking or scanty data, more inclusive strings were used to extend the research. When the output included an exceedingly large set of papers (e.g. Phase 2, primary aim; Phase 3, primary aim 1), the number of participants in each study was specified in the figures. The inclusion of relevant evidence based on personal knowledge or from the reference lists of pertinent

papers was admitted. Only papers written in English were included. The final selection of articles was based on relevance, as judged by the authors. The impact factor as such did not affect the selection of the papers included in the analysis. In the case of phases/aims evaluated as “Preliminary evidence”, personal knowledge about abstract presentations in international conferences was admitted. Two of the largest clinical trials databases were screened, more specifically the U.S. National Institutes of Health database (ClinicalTrials.gov) and the E.U. Clinical Trials Register from the European Medicines Agency (ClinicalTrialsRegister.eu) by using the keywords [“amyloid” AND (“positron emission tomography” OR “pet”)] and filtering only the ongoing clinical trials, in order to include up-to-date information in the review, especially concerning evidence from phase 4 and phase 5 studies that can be expected on a relatively short time basis.

3. Current clinical validity of amyloid-PET imaging

3.1 Phase 1 – Preclinical Exploratory Studies

Primary aim: To identify the rationale of the biomarker, based on pathology.

Amyloid plaques, whose main components are fibrillar aggregates of insoluble A β (Masters, et al., 1985), are considered essential neuropathological features of the histopathological diagnosis of AD (Hyman, et al., 2012). The data indicated that the PET ligands targeting fibrillar A β show high binding affinity to fibrillar A β in the nanomolar range (Choi, et al., 2009, Heurling, et al., 2016, Ni, et al., 2013, Rowe, et al., 2008) and favourable pharmacokinetics (Becker, et al., 2013, Choi, et al., 2009, Klunk, et al., 2004, Nelissen, et al., 2009, Price, et al., 2005, Wong, et al., 2010). This aim was considered fully achieved (Table 1, Fig. 1).

3.2 Phase 2 – Clinical Assay Development for Clinical Disease

3.2.1 Phase 2, primary aim: To estimate true and false positive rate and/or receiving operator characteristic (ROC) curve for the assay and assess its ability to distinguish subjects with and without disease.

A considerable number of studies assessed the accuracy of amyloid PET imaging in discriminating between clinically diagnosed AD dementia patients (McKhann, et al., 1984) and HCs. A specificity of 85% [with a 95% confidence interval (CI) of 81-88%] and a sensitivity of 88% (95% CI: 84-91%)

were estimated in a meta-analysis after pooling 19 studies (HC: n=510, AD: n=453) that used several ligands ($[^{11}\text{C}]\text{PIB}$ and $[^{18}\text{F}]$ ligands), different populations and several operating procedures for assessing the scans (visual rating scales or other quantification methods) (Frisoni, et al., 2013). Similar evidence was reported in a meta-analysis focussing on $[^{18}\text{F}]$ ligands (Yeo, et al., 2015). There was wide variability in the reported discriminative abilities of amyloid PET imaging in 36 studies using the clinical diagnosis of AD dementia as gold standard (Fig. 2 and Supplementary references 1). Conversely, when post-mortem histopathology was used to determine the presence of A β pathology (Braak and Braak, 1996, Hyman, et al., 2012, Hyman and Trojanowski, 1997, Mirra, et al., 1991) both the sensitivity and specificity of the discrimination reached or exceeded 90% (Clark, et al., 2012, Rinne, et al., 2012, Sabri, et al., 2015, Thurfjell, et al., 2014) (Fig. 2). This aim was considered fully achieved (Table 1, Fig. 1).

3.2.2 Phase 2, secondary aim 1: To optimise procedures for performing the assay and assess the reproducibility of the assay within and between laboratories.

The procedures related to amyloid PET imaging that require optimisation and standardisation include the comparability and reproducibility of the ligands, the operating procedures, and the methods of assessing the resulting scans.

The recently developed $[^{18}\text{F}]$ ligands florbetapir, flutemetamol and florbetaben bind to the same high affinity site as $[^{11}\text{C}]\text{PIB}$ (Ni, et al., 2013) and an excellent linear correlation was observed between the ligands when they were administered to the same individuals on separate scanning occasions (Adamczuk, et al., 2016, Hatashita, et al., 2014, Landau, et al., 2013a, Landau, et al., 2014, Vandenberghe, et al., 2010, Villemagne, et al., 2012, Wolk, et al., 2012). However the comparability of their respective discrimination abilities in the same population has been only preliminarily assessed (Wolk, et al., 2012).

Optimized procedures have been proposed regarding the synthesis of the different amyloid ligands (Liu, et al., 2010, Mathis, et al., 2003, Nelissen, et al., 2009, Rowe, et al., 2008) and test-retest studies have demonstrated the intra-individual reproducibility of the results (Joshi, et al., 2012, Price, et al., 2005, Rowe, et al., 2009, Vandenberghe, et al., 2010). However, the variety of ligands used and the variety of methods used to process the data (acquisition interval, reference

region, analysing procedure, partial volume correction) counters the direct comparability of the quantitative assessments. Nonetheless, recent efforts to standardise amyloid imaging methods resulted in a unified 0-100 scale of quantification, which can be used for all ligands. This implies that studies that use different amyloid PET ligands or methods of analysis can be compared using a common unit, the centiloid (Klunk, et al., 2015).

The FDA and EMA approved the clinical use of the new [^{18}F] amyloid PET ligands to assess patients with cognitive decline only with respect to visual interpretation. As a result, the pharmaceutical companies providing the ligands have developed specific guidelines and training reader programmes for nuclear medicine specialists, resulting in high inter-rater agreement with kappa values of 0.69-0.89 (Barthel, et al., 2011, Joshi, et al., 2012, Nayate, et al., 2015, Rinne, et al., 2012, Schreiber, et al., 2015, Wolk, et al., 2011). The inter-rater agreement for [^{11}C]PIB was also very high, with kappa = 0.96 (Rabinovici, et al., 2011). This aim was considered partly achieved (Table 1, Fig. 1).

3.2.3 Phase 2, secondary aim 2: To determine the relationship between biomarker measurements made in tissue (phase 1) and biomarker measurements made in noninvasive clinical specimens (phase 2).

Autopsy studies performed in patients who had undergone amyloid PET imaging *ante mortem* have illustrated the selective uptake of the amyloid ligands by fibrillar A β deposits, and the strong correlation between *in vivo* amyloid ligand retention and region-matched histopathological measures of A β pathology (Bacskai, et al., 2007, Clark, et al., 2012, Ikonomic, et al., 2008, Kadir, et al., 2011, Rinne, et al., 2012, Sabri, et al., 2015). The sensitivity and specificity of amyloid PET imaging in the detection of histopathologically confirmed A β pathology exceeds 90%, as discussed above (Clark, et al., 2012, Rinne, et al., 2012, Sabri, et al., 2015, Thurfjell, et al., 2014). Furthermore, the agreement between the cortical uptake of amyloid PET ligands and the histopathological phases of A β deposition, as determined by Thal, et al. (2002), has been recently illustrated (Murray, et al., 2015, Thal, et al., 2015). This aim was considered fully achieved (Table 1, Fig. 1).

3.2.4 Phase 2, secondary aim 3: To assess factors (e.g. gender, 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.

A β deposition increases in cognitively normal adults in an age-related manner (Villemagne, et al., 2011b) and some of these adults aged >60 years can exhibit pathological levels of cerebral fibrillar A β (i.e. they are “amyloid positive”) (Aizenstein, et al., 2008, Chetelat, et al., 2012, Fleisher, et al., 2013, Fleisher, et al., 2011, Jack, et al., 2014, Mielke, et al., 2012, Mintun, et al., 2006, Rowe, et al., 2010). More specifically, according to a recent meta-analysis, the number of amyloid-positive, cognitively normal individuals increases with age; >15% of individuals aged between 60 and 65 years and >30% of those aged 80 years or more are affected (Jansen, et al., 2015).

A β levels measured by amyloid PET are also significantly associated with ApoE4 status; the presence of the ApoE4 allele increases the age-related accumulation of A β , and increases by 2 to 3 times the prevalence of amyloid positivity (Fleisher, et al., 2013, Jansen, et al., 2015, Mielke, et al., 2012, Morris, et al., 2010, Murphy, et al., 2013, Reiman, et al., 2009, Rowe, et al., 2010).

A series of studies have attempted to investigate the association between gender and amyloid positivity but the results have not been consistent (Jansen, et al., 2015, Scheinin, et al., 2014). Similarly, inconsistent findings were reported on the role of education/cognitive activity in A β deposition as detected with PET imaging (Jansen, et al., 2015, Landau, et al., 2012a, Wirth, et al., 2014, Yasuno, et al., 2014).

The possibility of different thresholds for amyloid positivity in different subpopulations (according to age and ApoE4 status) will be addressed in on-going studies (Duara, et al., 2015). However, since both age and ApoE4 carrier status represent major risk factors for AD (Corder, et al., 1993), the applicability of different thresholds becomes questionable. This aim was considered partly achieved (Table 1, Fig. 1).

3.2.5 Phase 2, secondary aim 4: To assess factors (disease characteristics, in particular) associated with biomarker status or levels in diseased subjects.

Although the results regarding the role of age, independent of the ApoE4 carrier status, on the A β burden in clinically diagnosed AD dementia patients have been inconsistent (Chiotis, et al., 2015, Cho, et al., 2013, Choo, et al., 2011, Fleisher, et al., 2013, Johnson, et al., 2013b, Rabinovici, et al., 2010, Villemagne, et al., 2011b), a recent meta-analysis indicated a decrease in the prevalence of amyloid PET positivity with advancing age in clinically diagnosed AD patients (Ossenkoppele, et al., 2015).

This meta-analysis also reported a higher prevalence of amyloid positivity in ApoE4-positive AD dementia patients (Ossenkoppele, et al., 2015). However, several studies have shown inconclusive results regarding the effect of ApoE4 status on the cortical uptake of amyloid ligands in clinically diagnosed AD dementia patients (Drzezga, et al., 2009, Fleisher, et al., 2013, Johnson, et al., 2013b, Lehmann, et al., 2014, Ossenkoppele, et al., 2013b, Rowe, et al., 2010, Villemagne, et al., 2011b).

Associations between gender or educational attainment and amyloid positivity have not been consistently reported (Kemppainen, et al., 2008, Ossenkoppele, et al., 2015, Rowe, et al., 2010). This aim was considered partly achieved (Table 1, Fig. 1).

3.3 Phase 3 – Prospective Longitudinal Repository Studies

3.3.1 Phase 3, primary aim 1: To evaluate the capacity of biomarkers to detect the earliest disease stages.

A number of studies investigated the accuracy of amyloid PET imaging in discriminating between patients with MCI that will remain stable (considered to be non-AD-related impairment) and those with MCI progressing to AD dementia. A recent meta-analysis that included only [^{11}C]PIB PET studies with follow-up intervals of >24 months reported a pooled sensitivity of 96% (95% CI: 85-99%) and specificity of 72% (95% CI: 59-84%) (Ma, et al., 2014). Wide variability, however, is evident in the reported discriminative abilities of the different ligands in different cohorts, in studies that implemented different methodologies (Fig. 3, Supplementary references 2). Nonetheless, this aim was considered fully achieved (Table 1, Fig. 1).

3.3.2 Phase 3, primary aim 2: To define criteria for a positive biomarker test in preparation for phase 4 studies.

There is substantial agreement for several ligands between qualitative and quantitative assessment of the resulting scans (Cohen, et al., 2013, Schreiber, et al., 2015, Thurfjell, et al., 2014). Preliminary evidence, however, suggests that a combination of visual and quantitative evaluations of the scans could be the best approach (Cohen, et al., 2013, Nayate, et al., 2015, Schreiber, et al., 2015).

A variety of thresholds have been proposed for quantitatively defining amyloid positivity, and several groups have worked on defining neocortical thresholds for [^{11}C]PIB (Ewers, et al., 2012, Mormino, et al., 2009, Nordberg, et al., 2013, Rowe, et al., 2010), florbetapir (Chiotis, et al., 2015, Fleisher, et al., 2011, Joshi, et al., 2012, Mattsson, et al., 2014, Saint-Aubert, et al., 2014), flutemetamol (Leinonen, et al., 2014, Thurfjell, et al., 2014) and florbetaben (Villemagne, et al., 2011a). These attempts resulted in largely varying values for the individual ligands. Difficulties persist in the generation of a universal threshold, since amyloid PET imaging data are acquired and processed differently. The definition of the diseased population (clinical or pathological diagnosis) when determining amyloid positivity thresholds remains an open issue currently under debate and is another source of variability for the reported thresholds (Murray, et al., 2015, Nordberg, et al., 2013, Villeneuve, et al., 2015a).

The problem of the dichotomic lecture has been raised by some quantitative studies which suggest that 10-20% of patients have borderline values (Fleisher, et al., 2011), as well as by visual evaluation studies, indicating that borderline or uncertain values are also detected by visual assessment (Payoux, et al., 2015).

Finally, free or commercial tools have been developed for automated quantification analysis of amyloid PET imaging scans (e.g. CapAIBL [Computational Analysis of PET from AIBL], HERMES™ etc.). Due to the lack of standardization of the quantitative assessment as well as the number of borderline cases this aim was considered partly achieved (Table 1, Fig. 1).

3.3.3 Phase 3, secondary aim 1. To explore the impact of factors on the discriminatory abilities of the biomarker before clinical diagnosis.

At the time of writing this review no evidence was available from longitudinal studies investigating the impact of factors on the prediction ability of amyloid PET imaging in MCI patients and therefore this aim was considered as not achieved at the time of writing this review (Table 1, Fig. 1).

3.3.4 Phase 3, secondary aim 2. To compare markers with a view to selecting those that are most promising.

Amyloid imaging is more accurate than episodic memory measures for predicting progression from MCI to AD dementia (Ong, et al., 2015, Rowe, et al., 2013a).

Studies where several amyloid ligands have been used have demonstrated similar predictive accuracy for amyloid PET than for CSF measures of $A\beta_{1-42}$ (Leuzy, et al., 2015, Mattsson, et al., 2014) or of the ratios $A\beta_{1-42}/t\text{-tau}$ and $A\beta_{1-42}/p\text{-tau}_{181p}$ (Koivunen, et al., 2008, Leuzy, et al., 2015), although further studies are needed for validation purposes.

Measurement of medial temporal atrophy had poorer predictive accuracy than amyloid PET with respect to conversion to AD dementia (Ong, et al., 2015, Rowe, et al., 2013a, Thurfjell, et al., 2012), probably because of the lower sensitivity of magnetic resonance imaging (MRI) volume measurements in comparison to the cortical uptake of amyloid ligands (Trzepacz, et al., 2014, Vandenberghe, et al., 2013).

Trzepacz, et al. (2014) showed that amyloid imaging is more sensitive and [^{18}F]FDG is more specific in the prediction of MCI progression to AD dementia. However, data comparing the overall predictive accuracy of [^{18}F]FDG PET with that of amyloid PET imaging are inconclusive (Bruck, et al., 2013, Landau, et al., 2012b).

To the best of our knowledge, no study has yet attempted to compare the prediction accuracy of amyloid PET imaging with that of [^{123}I]-Ioflupane or [^{123}I]-MIBG imaging in the MCI population. Consequently, this aim was considered partly achieved (Table 1, Fig. 1).

3.3.5 Phase 3, secondary aim 3. To develop algorithms for positivity based on combinations of markers.

Studies investigating the combination of episodic memory measures with amyloid PET imaging in MCI patients have given inconsistent results with respect to improved predictive accuracy (Ong, et

al., 2015, Rowe, et al., 2013a). However, the fact that by definition MCI patients already present with cognitive impairment limits the relevance of the use of cognitive measurements in combination with PET.

Although one study reported that the addition of medial temporal atrophy measures did not improve the predictive accuracy of amyloid PET imaging (Ong, et al., 2015), other studies indicated that amyloid imaging plus structural MRI provides the best prediction accuracy over all other imaging modalities, alone or in combination (Rowe, et al., 2013a, Trzepacz, et al., 2014). Moreover, a reduced hippocampal volume seems to predict faster progression to AD dementia in MCI patients with a positive amyloid PET scan (Jack, et al., 2010, Thurfjell, et al., 2012).

Preliminary evidence indicates that combining [^{18}F]FDG PET with amyloid PET improves the prediction accuracy of amyloid PET alone (Bruck, et al., 2013, Ossenkoppele, et al., 2013a).

To the best of our knowledge, no study has yet attempted to combine CSF measures, [^{123}I]-loflupane imaging or [^{123}I]-MIBG imaging with amyloid PET imaging to define their prediction accuracy. This aim was considered partly achieved (Table 1, Fig. 1).

3.3.6 Phase 3, secondary aim 4. To determine a biomarker testing interval for phase 4 studies if repeated testing is of interest.

At the time of writing this review, evidence from a case series of MCI patients supports the notion that repeated amyloid PET scans would be of interest in MCI amyloid-negative individuals at baseline (Kemppainen, et al., 2014, Koivunen, et al., 2011). More specifically Kemppainen, et al. (2014) observed that the A β burden of MCI patients who had a negative initial amyloid PET scan exceeded the threshold at the follow-up investigation (after a five-year delay) and finally developed AD dementia. This view is reinforced by the finding that an A β burden at levels below but close to the applied thresholds could be of clinical relevance (Villeneuve, et al., 2015a), and that those levels tend to increase over time (Villeneuve, et al., 2015b). Consequently, only preliminary evidence is available regarding the aim of determining a relevant biomarker-testing interval for amyloid-PET (Table 1, Fig. 1).

3.4 Phase 4 – Prospective Diagnostic Studies

3.4.1 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.

At the time of writing this review no evidence was available, and therefore, this aim was considered as not achieved. However seven on-going clinical trials were identified that are likely to provide evidence on a short time basis (2012-001599-12,2014-000562-21,NCT01518374,NCT02353949,NCT02420756,NCT02681172,NCT02778971).

3.4.2 Secondary aim 1: To describe the characteristics of disease detected by the biomarker test—in particular, with regard to the potential benefits incurred of early detection.

This aim had not been achieved at the time of writing this review.

3.4.3 Secondary aim 2: To assess the practical feasibility of implementing the case finding program and the compliance of test-positive subjects with work-up and treatment recommendations.

This aim had not been achieved at the time of writing this review.

3.4.4 Secondary aim 3: To make preliminary assessments of the effects of biomarker testing on costs and mortality associated with the disease.

Preliminary data on clinical diagnoses incorporating amyloid PET imaging suggests high accuracy with regard to *post-mortem* confirmation (Sanchez-Juan, et al., 2014). This could lead to decreased medical costs in terms of assessment and incorrect treatment of patients. However, with respect to the specific aim of assessing the effects of biomarker testing on costs and mortality in a routine clinical MCI population, no evidence is available. This aim had not been achieved at the time of writing this review (Table 1, Fig. 1).

3.4.5 Secondary aim 4: To monitor disease occurring clinically but not detected by the biomarker testing protocol.

This aim had not been achieved at the time of writing this review.

3.5 Phase 5 – Alzheimer Control Studies

This phase can only be properly carried out when an effective, accepted treatment is available. In the field of AD, only mortality and quality of life should be considered in this phase. The aims of this phase had not been achieved at the time of writing this review.

4. Conclusions

We carried out this review as part of a broader objective that aims to accelerate the use of biomarkers in the clinic for the diagnosis of AD at the pre-dementia stage, where differentiating AD from non-AD causes of cognitive impairment is of huge clinical and social relevance. To this end, we used a biomarker validation framework developed for oncology biomarkers (Pepe, et al., 2001) which ultimately took inspiration from the traditional phases of drug development. We adapted the oncology framework to the pre-dementia AD context, and used it to highlight issues that have been sufficiently investigated and those that need more research. This will allow funders and other actors in biomedical research to prioritise research topics appropriately in the path towards achievement of the ultimate aim of appropriate, effective, efficient use of AD biomarkers in the clinic.

In this review, we examined the available evidence and assessed the progress of assessment of amyloid PET imaging in the light of the five-phase framework. It appears that, since the emergence of amyloid PET imaging, there has been much investigation of its ability to specifically target AD (Phase 2) and to predict the conversion of MCI to AD dementia (Phase 3). These efforts have resulted to a large extent in the achievement of the three first phases of the biomarker development framework. At the same time, attempts to standardise the evaluation of amyloid PET imaging and to compare its outcomes with those of other AD biomarkers are on-going, the associated aims being so far only partly achieved. Large prospective amyloid PET imaging studies of routine patients presenting with MCI (Phase 4), which will lead to a diagnosis [prodromal AD (Dubois, et al., 2014) or MCI due to AD (Albert, et al., 2011)] and to the treatment of patients rated as amyloid positive, are now needed. Such studies are currently on-going. They will help to determine the accuracy of amyloid PET imaging in MCI patients in the clinic, and to

evaluate the feasibility of its use along with its clinical impact and associated costs. Of note, for the sake of clarity, evidence from [^{11}C]PIB and all approved [^{18}F] ligands were considered equally in this review.

The accessibility of patients to amyloid PET imaging has increased with the introduction of the [^{18}F] ligands, but the process nonetheless remains mainly limited to academic centres with adequate funding. The costs of performing amyloid PET scans in a clinical setting are high and, to date, are reimbursed by nearly no insurance company worldwide, although a series of investigations are currently underway to estimate the cost-effectiveness of this process (NCT02420756). Therefore, although recommendations for appropriate-use criteria for amyloid PET are available (Johnson, et al., 2013a), they are no substitute for evidence-based guidelines for the clinical use of the biomarker in the assessment of AD (Booij, et al., 2013). These guidelines, which would take all available biomarkers and covariates into account, would identify the target populations which would benefit the most from the use of amyloid PET imaging (based on patient demographics, genetic information or other biomarkers).

To date, the problem of standardising the development of amyloid PET imaging and other biomarkers of AD has received scant attention. The Geneva Task Force has used a unique, systematic approach to harmonise the differential development of biomarkers in a common framework, with the aim of proposing a roadmap for the rational translation of AD biomarkers to the clinical setting. This approach allows the identification of the stage of progress of investigations into each biomarker as well as of comparisons between them. Greater progress appears to have been made in the clinical validation of amyloid PET imaging than of measures of episodic memory (Cerami, et al., in this issue), [^{123}I]-Ioflupane imaging or [^{123}I]-MIBG imaging (Sonni, et al., in this issue) in the five-phase framework, while less progress has been made in comparison with CSF measures (Mattsson, et al., in this issue), medial temporal atrophy (Ten Kate, et al., in this issue) and [^{18}F]FDG PET imaging (Garibotto, et al., in this issue). The few available studies that directly compared the performance of the available biomarkers, in terms of predictive ability, have also been identified. These indicate that amyloid PET imaging, as a pathophysiological marker of AD (Dubois, et al., 2014), is more sensitive than the other markers, but is only moderately specific. Although the results are very preliminary, the studies that combined two different biomarkers – as

proposed by the recent criteria for MCI (Albert, et al., 2011) – found that the specificity of amyloid PET imaging was improved when it was combined with a topographical biomarker for AD ([¹⁸F]FDG PET or medial temporal atrophy measures) (Bruck, et al., 2013, Ossenkoppele, et al., 2013a, Rowe, et al., 2013a, Trzepacz, et al., 2014). A note of caution is due when comparing or combining episodic memory measures with other AD biomarkers, since cognitive function constitutes both a biomarker and the selection criterion of the investigated subjects in the present framework.

The development of A β biomarkers has been central in AD research since the formulation of the amyloid cascade hypothesis, the most widely accepted conceptualisation of the disease pathogenesis. The present effort assessed in parallel reviews the clinical validity of two biomarkers of A β pathology, namely amyloid PET imaging and A β markers in the CSF. PET allows the visualisation of the regional distribution of A β pathology in a standardised manner, while CSF sampling is considered as a more affordable and easily accessible technique. However, a much debated question is whether the two biomarkers could be considered interchangeable (Blennow, et al., 2015, Landau, et al., 2013b, Leuzy, et al., 2016). Considerably more work will need to be done to determine the relationship between the two biomarkers.

This review is limited in that, notwithstanding our efforts to be as inclusive as possible, the literature search was not conducted as a formal systematic review. A number of PubMed research strings were proposed centrally for the whole project, but the literature databases and some paper selection criteria were chosen by the individual authors, who could add papers from personal knowledge or from the reference lists of other papers. Nonetheless, the authors are confident that the review covers all the most relevant papers on the topic. The scope of this effort was limited to the following biomarkers: episodic memory measures, CSF measures, medial temporal atrophy, [¹⁸F]FDG PET, [¹²³I]-loflupane imaging and [¹²³I]-MIBG imaging; and therefore neither comparisons or combination of amyloid PET imaging with other markers (e.g. plasma markers) nor combination with useful information provided by relevant risk factors (e.g. ApoE status) were reviewed in the present work. Further, while the original framework Pepe, et al. (2001) was developed to screen for cancer in asymptomatic populations, the roadmap to the systematic validation of the biomarkers for AD is at the moment restricted, mainly because of the lack of an effective treatment, to the

early, symptomatic stage of the disease, e.g. at the MCI due to AD (Albert, et al., 2011) or prodromal AD stages (Dubois, et al., 2014). Future developments in the field of AD and in AD drug development may require and allow the extension of this framework to include asymptomatic preclinical patients. Thus, the nature of the work may well change in the near future; however, it remains necessary for the present to proceed as far as possible in this direction in order to improve clinical practice in the AD field.

5. Acknowledgements

The Geneva Task Force for the Roadmap of Alzheimer's Biomarkers includes the participants in a workshop held in Geneva on December 8-9, 2014. The principal investigator (PI) of the Geneva Roadmap effort is Giovanni B Frisoni, with Bengt Winblad and Clifford R Jack Jr as co-PIs. The task force includes experts in biomarker development from the oncology community; experts in diagnostic AD biomarkers from Switzerland and Europe; representatives of pertinent scientific societies (Federation of European Societies of Neuropsychology - FENS, European Nuclear Society - ENS, International Foundation of Clinical Chemistry and Laboratory Medicine - IFCCLM, European Association of Nuclear Medicine - EANM, and Swiss Federation of Clinical Neuro Societies - SFCNS); representatives of patient advocate, bioethicist and regulatory agencies, and early career researchers. The Geneva Task Force has been endorsed by the EADC – European Alzheimer's Disease Consortium.

The workshop was funded by a competitive grant from the Swiss National Science Foundation and unrestricted grants from: Alzheimer Forum Switzerland; Association pour la Recherche sur Alzheimer, Genève; Piramal; Eli Lilly & Company; General Electric; Guerbet; TEVA Pharma; Academie Suisse de Sciences Médicales; Vifor Pharma Switzerland; Novartis; Siemens; and IXICO. The Alzheimer's Association hosted the first follow-up meeting of the initiative at the 2015 AAIC congress in Washington. We acknowledge the help from Margherita Mauri and Daria Gennaro (IRCCS Fatebenefratelli, Brescia, Italy) and Agnese Picco (Università di Genova, Genova, Italy) who took care of the logistics of the workshop.

The following scientific societies took part in the Geneva Workshop for the Roadmap of Alzheimer's Biomarkers on December 8-9 2014. Flavio Nobili was delegate from the European

Association of Nuclear Medicine (EANM) Neuroimaging Committee. Kaj Blennow was delegate and Chair of the International Federation of Clinical Chemistry and Laboratory Medicine Working Group for CSF proteins (IFCC WG-CSF). Frederik Barkhof was delegate from the European Society of Neuroradiology (ESNR). Stefano Cappa was delegate and Chair of the Federation of European Societies of Neuropsychology (FENS). Urs Mosimann was delegate from the Swiss Federation of Clinical Neuro Societies (SFCNS). The content of this paper represents the opinion of the individual authors and is not necessarily endorsed by the scientific societies, which took part in the Geneva Workshop for the Roadmap of Alzheimer's Biomarkers.

The authors K.C., L.S.A. and A.N. are financially funded by the Swedish Research Council (project 05817), the Swedish Brain Power, the Swedish Foundation for Strategic Research (SSF) and the Wenner-Gren Foundation.

6. Disclosure statement

Marina Boccardi received a research grant from Piramal and served in an advisory board for Lilly. Valentina Garibotto received speaker honoraria from GE Healthcare and Eli-Lilly & Co. Flavio Nobili has received honoraria for teaching courses on amyloid PET from Eli-Lilly & Co. Agneta Nordberg has participated in advisory board for GE Healthcare, Piramal, Amyvid, received honorarium for lectures from Novartis, GE Healthcare, and research grant (unrestricted) from GE Healthcare. The other authors declare no conflict of interest relating to the material presented in this article.

7. Figures and Tables:

Development of **amyloid PET** adapted from the framework of Pepe et al. 2001

Phase 1: Rationale for the use of amyloid PET	Phase 2: Discrimination ability of amyloid PET		Phase 3: Detection ability in early phase		Phase 4: Amyloid PET accuracy in representative MCI patients		Phase 5: Impact of amyloid PET-based diagnosis on relevant outcomes					
Primary aim	Primary aim	Secondary aims	Primary aims	Secondary aims	Primary aim	Secondary aims	Primary aim	Secondary aims				
Potential leads	Identify discrimination accuracy AD/HC	Assay definition	Assess capacity of earliest (MCI) detection	Impact of covariates	Assess true/false referral rate in amyloid PET diagnosed patients	Detect predictive features	Estimate impact on morbidity & disability	Cost/benefit quantification				
		Ante mortem/autopsy		Compare markers		Practical feasibility		Compliance in different settings				
		Covariates in HC	Criteria for positivity	Combine markers		Estimate impact & costs		Compare different protocols				
		Covariates in AD		Determine testing Interval		Monitor false negatives						
<div>Achievement</div> <table><tr><td>Full</td><td>Partial</td></tr><tr><td>Preliminary</td><td>Not achieved</td></tr></table>		Full	Partial	Preliminary	Not achieved							
Full	Partial											
Preliminary	Not achieved											

Figure 1. Synopsis of the clinical validity of amyloid PET imaging as adapted from an oncology framework (Pepe, et al., 2001). AD=Alzheimer's disease; HC=Healthy Controls; MCI: mild cognitive impairment; PA: primary aim; PET: positron emission tomography; SA: Supplementary aim.

Figure 2. Sensitivity - False Positive Rate graph showing the ability of amyloid PET to discriminate between healthy controls and Alzheimer's disease patients (Supplementary references 1).

Figure 3. Sensitivity - False Positive Rate graph showing the ability of amyloid PET to discriminate between patients with mild cognitive impairment that will remain stable and those with mild cognitive impairment progressing to Alzheimer's disease dementia (Supplementary references 2).

Phase - Design	General Aim	Specific Aims		Progress	Evidence in AD
1 – Preclinical Exploratory Studies	Identify the rationale of amyloid PET imaging, based on pathology	Primary:	To identify leads for potentially useful amyloid PET ligands and prioritise identified leads	Amyloid plaques, containing fibrillar amyloid-beta, are essential neuropathological features of the histopathological diagnosis of AD.	Fully Achieved
2 – Clinical Assay Development for Clinical Disease	Define the ability of amyloid PET imaging to discriminate patients from controls	Primary:	To estimate TPR and FPR or ROC curves for the assay and to assess its ability to distinguish between subjects with and without disease	Case-control studies show good sensitivity (85%) and specificity (88%) for amyloid PET imaging discrimination between clinically diagnosed AD dementia patients and healthy controls. The sensitivity and specificity when using histopathology as gold standard reach 90%.	Fully Achieved
		Secondary 1:	To optimise procedures for performing amyloid PET imaging and to assess its reproducibility within and between centres.	Procedures for amyloid PET ligand synthesis, PET acquisition and visual evaluation of the scans have to a large extent been optimised and standardised. Efforts are on-going to standardise the quantification methods used.	Partly Achieved
		Secondary 2:	To determine the relationship between amyloid-beta measurements made in tissue (phase 1) and amyloid PET imaging measurements made on a noninvasive clinical specimen (phase 2)	The selective binding of amyloid ligands to fibrillar amyloid-beta has been illustrated as well as the strong correlation between the <i>ante-mortem</i> cortical uptake and <i>post-mortem</i> quantification studies.	Fully Achieved
		Secondary 3:	To assess factors (e.g. sex, age, etc.), associated with amyloid PET status or level in control subjects. If such factors affect amyloid PET, thresholds for test positivity may need to be defined separately for target subpopulations.	The prevalence of amyloid positivity in control subjects is related to increasing age and the presence of the ApoE4 allele. On-going studies are investigating the use of thresholds adjusted for age and ApoE4 status.	Partly Achieved
		Secondary 4:	To assess factors, particularly disease characteristics, associated with amyloid PET status or level in diseased subjects.	The prevalence of amyloid positivity in clinically diagnosed AD patients decreases with increasing age and in the absence of the ApoE4 allele.	Partly Achieved
3 – Prospective Longitudinal Repository Studies	Define the ability of amyloid PET imaging to detect the disease in its early phase	Primary 1:	To evaluate the capacity of amyloid PET imaging to detect the earliest disease stages	Excellent sensitivity (96%) and moderate specificity (72%) have been reported for amyloid PET imaging discrimination between patients with MCI that remains stable and those with MCI progressing to clinically diagnosed AD dementia.	Fully Achieved
		Primary 2:	To define criteria for an amyloid PET-positive scan in preparation for phase 4.	Criteria for qualitative assessment are established. On-going studies aim to establish standardised quantitative criteria across different centres.	Partly Achieved
		Secondary 1:	To explore the impact of factors on the discriminatory abilities of amyloid PET imaging before clinical diagnosis.	n/a	Not Achieved
		Secondary 2:	To compare BM/s with a view to selecting those that are most promising	Direct comparisons of core BM/s indicate that amyloid PET imaging is probably the most sensitive but has only moderate specificity.	Partly Achieved
		Secondary 3:	To develop algorithms for positivity based on combinations of BM/s.	Combinations of two core BM/s indicate that addition of medial temporal atrophy measures or [¹⁸ F]FDG PET imaging could improve the specificity of amyloid PET imaging.	Partly Achieved

		Secondary 4:	To determine an amyloid PET testing interval for phase 4 studies if repeated testing is of interest.	On-going studies aim to determine whether repeated amyloid PET imaging would be of interest in amyloid-negative patients at baseline.	Preliminary Evidence
4 – Prospective Diagnostic Studies	Quantify the amyloid PET imaging accuracy and usefulness in patients whose diagnosis and treatment is based on the amyloid PET status.	Primary:	To determine the operating characteristics of amyloid PET imaging 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.	n/a	Not Achieved
		Secondary 1:	To describe the characteristics of disease detected by amyloid PET imaging—in particular, with regard to the potential benefits of early detection.	n/a	Not Achieved
		Secondary 2:	To assess the practical feasibility of implementing the diagnostic program and the compliance of test-positive subjects with work-up and treatment recommendations.	n/a	Not Achieved
		Secondary 3:	To make preliminary assessments of the effects of amyloid PET imaging on costs and mortality associated with the disease.	n/a	Not Achieved
		Secondary 4:	To monitor disease occurring clinically but not detected by amyloid PET imaging.	n/a	Not Achieved
5 – Disease Control Studies	Quantify the impact of the amyloid PET imaging-based diagnosis on clinically meaningful outcomes and costs.	Primary:	To estimate the reductions in disease-associated mortality, morbidity, and disability afforded by amyloid PET imaging.	n/a	Not Achieved
		Secondary 1:	To obtain information about the costs of amyloid PET imaging and treatment and the cost per life saved or per quality-adjusted life year.	n/a	Not Achieved
		Secondary 2:	To evaluate compliance with testing and work-up in a diverse range of settings.	n/a	Not Achieved
		Secondary 3:	To compare different amyloid PET imaging protocols and/or to compare different approaches to treating test positive subjects with regard to effects on mortality and costs.	n/a	Not Achieved

Table 1. Available or required evidence indicating full, partial or lack of achievement of the biomarker phases adapted from the oncology framework (Pepe, et al., 2001) for amyloid PET imaging. AD = Alzheimer's disease; ApoE4 = apolipoprotein E ε4; BM/s = biomarkers; FPR = false-positive rate; n/a = not available; PET = positron emission tomography; ROC = receiving operator characteristic; TPR = true-positive rate.

8. References:

- 2012-001599-12. The clinical value of amyloid imaging with [18F]-AV45 in a population of memory clinic patients. In: ClinicalTrialsRegisteru [Internet] London: European Medicines Agency (UK) 1995-2016 Available from: <https://www.clinicaltrialsregisteru/ctr-search/trial/2012-001599-12/NL#summary>, VU University Medical Center.
- 2014-000562-21. Amyloid-PET as a diagnostic marker in daily practice. In: ClinicalTrialsRegisteru [Internet] London: European Medicines Agency (UK) 1995-2016 Available from: <https://www.clinicaltrialsregisteru/ctr-search/trial/2014-000562-21/NL>, VU University Medical Center.
- Adamczuk, K., Schaefferbeke, J., Nelissen, N., Neyens, V., Vandenbulcke, M., Goffin, K., Lilja, J., Hilven, K., Dupont, P., Van Laere, K., Vandenberghe, R. 2016. Amyloid imaging in cognitively normal older adults: comparison between (18)F-flutemetamol and (11)C-Pittsburgh compound B. *European journal of nuclear medicine and molecular imaging* 43(1), 142-51. doi:10.1007/s00259-015-3156-9.
- Agdeppa, E.D., Kepe, V., Liu, J., Flores-Torres, S., Satyamurthy, N., Petric, A., Cole, G.M., Small, G.W., Huang, S.C., Barrio, J.R. 2001. Binding characteristics of radiofluorinated 6-dialkylamino-2-naphthylethylidene derivatives as positron emission tomography imaging probes for beta-amyloid plaques in Alzheimer's disease. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 21(24), RC189.
- Aizenstein, H.J., Nebes, R.D., Saxton, J.A., Price, J.C., Mathis, C.A., Tsopelas, N.D., Ziolkowski, S.K., James, J.A., Snitz, B.E., Houck, P.R., Bi, W., Cohen, A.D., Lopresti, B.J., DeKosky, S.T., Halligan, E.M., Klunk, W.E. 2008. Frequent amyloid deposition without significant cognitive impairment among the elderly. *Archives of neurology* 65(11), 1509-17. doi:10.1001/archneur.65.11.1509.
- Albert, M.S., DeKosky, S.T., Dickson, D., Dubois, B., Feldman, H.H., Fox, N.C., Gamst, A., Holtzman, D.M., Jagust, W.J., Petersen, R.C., Snyder, P.J., Carrillo, M.C., Thies, B., Phelps, C.H. 2011. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 7(3), 270-9. doi:10.1016/j.jalz.2011.03.008.
- Bacskaï, B.J., Frosch, M.P., Freeman, S.H., Raymond, S.B., Augustinack, J.C., Johnson, K.A., Irizarry, M.C., Klunk, W.E., Mathis, C.A., DeKosky, S.T., Greenberg, S.M., Hyman, B.T., Growdon, J.H. 2007. Molecular imaging with Pittsburgh Compound B confirmed at autopsy: a case report. *Archives of neurology* 64(3), 431-4. doi:10.1001/archneur.64.3.431.
- Barthel, H., Luthardt, J., Becker, G., Patt, M., Hammerstein, E., Hartwig, K., Eggers, B., Sattler, B., Schildan, A., Hesse, S., Meyer, P.M., Wolf, H., Zimmermann, T., Reischl, J., Rohde, B., Gertz, H.J., Reiningner, C., Sabri, O. 2011. Individualized quantification of brain beta-amyloid burden: results of a proof of mechanism phase 0 florbetaben PET trial in patients with Alzheimer's disease and healthy controls. *European journal of nuclear medicine and molecular imaging* 38(9), 1702-14. doi:10.1007/s00259-011-1821-1.
- Becker, G.A., Ichise, M., Barthel, H., Luthardt, J., Patt, M., Seese, A., Schultze-Mosgau, M., Rohde, B., Gertz, H.J., Reiningner, C., Sabri, O. 2013. PET quantification of 18F-florbetaben binding to beta-amyloid deposits in human brains. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* 54(5), 723-31. doi:10.2967/jnumed.112.107185.
- Bennett, D.A., Wilson, R.S., Schneider, J.A., Evans, D.A., Beckett, L.A., Aggarwal, N.T., Barnes, L.L., Fox, J.H., Bach, J. 2002. Natural history of mild cognitive impairment in older persons. *Neurology* 59(2), 198-205.
- Blennow, K., Mattsson, N., Scholl, M., Hansson, O., Zetterberg, H. 2015. Amyloid biomarkers in Alzheimer's disease. *Trends in pharmacological sciences* 36(5), 297-309. doi:10.1016/j.tips.2015.03.002.
- Boccardi, M., Gallo, V., Yutaka, Y., Vineis, P., Padovani, A., Mosimann, U., Giannakopoulos, P., Gold, G., Dubois, B., Jack, C.R., Winblad, B., Frisoni, G.B., Albanese, E., Biomarkers, a.t.G.T.F.f.t.R.o.A.s. in this issue. The Biomarker-based Diagnosis of Alzheimer's Disease. 2 – Lessons From Oncology. *Neurobiology of aging*.
- Booij, J., Arbizu, J., Darcourt, J., Hesse, S., Nobili, F., Payoux, P., Pappata, S., Tatsch, K., Walker, Z., Pagani, M. 2013. Appropriate use criteria for amyloid PET imaging cannot replace guidelines: on behalf of the European Association of Nuclear Medicine. *European journal of nuclear medicine and molecular imaging* 40(7), 1122-5. doi:10.1007/s00259-013-2415-x.
- Braak, H., Braak, E. 1996. Evolution of the neuropathology of Alzheimer's disease. *Acta neurologica Scandinavica Supplementum* 165, 3-12.
- Bruck, A., Virta, J.R., Koivunen, J., Koikkalainen, J., Scheinin, N.M., Helenius, H., Nagren, K., Helin, S., Parkkola, R., Viitanen, M., Rinne, J.O. 2013. [11C]PIB, [18F]FDG and MR imaging in patients with mild cognitive impairment. *European journal of nuclear medicine and molecular imaging* 40(10), 1567-72. doi:10.1007/s00259-013-2478-8.
- Cerami, C., Dubois, B., Boccardi, M., Monsch, A.U., Demonet, J.F., Cappa, S.F., Biomarkers, a.t.G.T.F.f.t.R.o.A.s. in this issue. Clinical validity of free and cued wordlist recall as a gateway-biomarker for Alzheimer's disease in the context of a structured 5-phase development framework. *Neurobiology of aging*.
- Chetelat, G., Villemagne, V.L., Villain, N., Jones, G., Ellis, K.A., Ames, D., Martins, R.N., Masters, C.L., Rowe, C.C., Group, A.R. 2012. Accelerated cortical atrophy in cognitively normal elderly with high beta-amyloid deposition. *Neurology* 78(7), 477-84. doi:10.1212/WNL.0b013e318246d67a.
- Chiotis, K., Carter, S.F., Farid, K., Savitcheva, I., Nordberg, A., Netow, D.M.I.D., Initi, A.s.D.N. 2015. Amyloid PET in European and North American cohorts; and exploring age as a limit to clinical use of amyloid imaging. *European journal of nuclear medicine and molecular imaging* 42(10), 1492-506. doi:10.1007/s00259-015-3115-5.
- Cho, H., Seo, S.W., Kim, J.H., Suh, M.K., Lee, J.H., Choe, Y.S., Lee, K.H., Kim, J.S., Kim, G.H., Noh, Y., Ye, B.S., Kim, H.J., Yoon, C.W., Chin, J., Na, D.L. 2013. Amyloid deposition in early onset versus late onset Alzheimer's disease. *Journal of Alzheimer's disease : JAD* 35(4), 813-21. doi:10.3233/JAD-121927.
- Choi, S.R., Golding, G., Zhuang, Z., Zhang, W., Lim, N., Hefti, F., Benedum, T.E., Kilbourn, M.R., Skovronsky, D., Kung, H.F. 2009. Preclinical properties of 18F-AV-45: a PET agent for Abeta plaques in the brain. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* 50(11), 1887-94. doi:10.2967/jnumed.109.065284.
- Choo, I.H., Lee, D.Y., Kim, J.W., Seo, E.H., Lee, D.S., Kim, Y.K., Kim, S.G., Park, S.Y., Woo, J.I., Yoon, E.J. 2011. Relationship of amyloid-beta burden with age-at-onset in Alzheimer disease. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry* 19(7), 627-34. doi:10.1097/JGP.0b013e318202bf3a.
- Clark, C.M., Pontecorvo, M.J., Beach, T.G., Bedell, B.J., Coleman, R.E., Doraiswamy, P.M., Fleisher, A.S., Reiman, E.M., Sabbagh, M.N., Sadowsky, C.H., Schneider, J.A., Arora, A., Carpenter, A.P., Flitter, M.L., Joshi, A.D., Krautkramer, M.J., Lu, M., Mintun, M.A., Skovronsky, D.M., Group, A.-A.S. 2012. Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-beta plaques: a prospective cohort study. *The Lancet Neurology* 11(8), 669-78. doi:10.1016/S1474-4422(12)70142-4.

- Cohen, A.D., Mowrey, W., Weissfeld, L.A., Aizenstein, H.J., McDade, E., Mountz, J.M., Nebes, R.D., Saxton, J.A., Snitz, B., Dekosky, S., Williamson, J., Lopez, O.L., Price, J.C., Mathis, C.A., Klunk, W.E. 2013. Classification of amyloid-positivity in controls: comparison of visual read and quantitative approaches. *NeuroImage* 71, 207-15. doi:10.1016/j.neuroimage.2013.01.015.
- Corder, E.H., Saunders, A.M., Strittmatter, W.J., Schmechel, D.E., Gaskell, P.C., Small, G.W., Roses, A.D., Haines, J.L., Pericak-Vance, M.A. 1993. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 261(5123), 921-3.
- Drzezga, A., Grimmer, T., Henriksen, G., Muhlau, M., Perneczky, R., Miederer, I., Praus, C., Sorg, C., Wohlschläger, A., Riemenschneider, M., Wester, H.J., Foerstl, H., Schwaiger, M., Kurz, A. 2009. Effect of APOE genotype on amyloid plaque load and gray matter volume in Alzheimer disease. *Neurology* 72(17), 1487-94. doi:10.1212/WNL.0b013e3181a2e8d0.
- Duara, R., Barker, W., Loewenstein, D., Greig, M., Rodriguez, R., Goryawala, M., Zhou, Q., Adjouadi, M. 2015. Should the threshold for a positive amyloid pet scan be adjusted for ApoE carrier status, age, level of cognitive and functional impairment? 9th Human Amyloid Imaging meeting, Miami, U.S.A., pp P19.
- Dubois, B., Feldman, H.H., Jacova, C., Hampel, H., Molinuevo, J.L., Blennow, K., DeKosky, S.T., Gauthier, S., Selkoe, D., Bateman, R., Cappa, S., Crutch, S., Engelborghs, S., Frisoni, G.B., Fox, N.C., Galasko, D., Habert, M.O., Jicha, G.A., Nordberg, A., Pasquier, F., Rabinovici, G., Robert, P., Rowe, C., Salloway, S., Sarazin, M., Epelbaum, S., de Souza, L.C., Vellas, B., Visser, P.J., Schneider, L., Stern, Y., Scheltens, P., Cummings, J.L. 2014. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *The Lancet Neurology* 13(6), 614-29. doi:10.1016/S1474-4422(14)70090-0.
- Ewers, M., Insel, P., Jagust, W.J., Shaw, L., Trojanowski, J.Q., Aisen, P., Petersen, R.C., Schuff, N., Weiner, M.W., Alzheimer's Disease Neuroimaging, I. 2012. CSF biomarker and PIB-PET-derived beta-amyloid signature predicts metabolic, gray matter, and cognitive changes in nondemented subjects. *Cerebral cortex* 22(9), 1993-2004. doi:10.1093/cercor/bhr271.
- Fleisher, A.S., Chen, K., Liu, X., Ayutyanont, N., Roontiva, A., Thiyyagura, P., Protas, H., Joshi, A.D., Sabbagh, M., Sadowsky, C.H., Sperling, R.A., Clark, C.M., Mintun, M.A., Pontecorvo, M.J., Coleman, R.E., Doraiswamy, P.M., Johnson, K.A., Carpenter, A.P., Skovronsky, D.M., Reiman, E.M. 2013. Apolipoprotein E epsilon4 and age effects on florbetapir positron emission tomography in healthy aging and Alzheimer disease. *Neurobiology of aging* 34(1), 1-12. doi:10.1016/j.neurobiolaging.2012.04.017.
- Fleisher, A.S., Chen, K., Liu, X., Roontiva, A., Thiyyagura, P., Ayutyanont, N., Joshi, A.D., Clark, C.M., Mintun, M.A., Pontecorvo, M.J., Doraiswamy, P.M., Johnson, K.A., Skovronsky, D.M., Reiman, E.M. 2011. Using positron emission tomography and florbetapir F18 to image cortical amyloid in patients with mild cognitive impairment or dementia due to Alzheimer disease. *Archives of neurology* 68(11), 1404-11. doi:10.1001/archneurol.2011.150.
- Frisoni, G.B., Bocchetta, M., Chetelat, G., Rabinovici, G.D., de Leon, M.J., Kaye, J., Reiman, E.M., Scheltens, P., Barkhof, F., Black, S.E., Brooks, D.J., Carrillo, M.C., Fox, N.C., Herholz, K., Nordberg, A., Jack, C.R., Jr., Jagust, W.J., Johnson, K.A., Rowe, C.C., Sperling, R.A., Thies, W., Wahlund, L.O., Weiner, M.W., Pasqualetti, P., Decarli, C., Area, I.S.s.N.P.I. 2013. Imaging markers for Alzheimer disease: which vs how. *Neurology* 81(5), 487-500. doi:10.1212/WNL.0b013e31829d86e8.
- Frisoni, G.B., Perani, D., Bastianello, S., Bernardi, G., Porteri, C., Boccardi, M., Cappa, S.F., Trabucchi, M., Padovani, A. in this issue. A roadmap to the use of biomarkers for the diagnosis of Alzheimer's disease in clinical practice: the Italian inter-societal consensus. *Neurobiology of aging*.
- Garibotto, V., Herholz, K., Boccardi, M., Picco, A., Varrone, A., Nordberg, A., Nobili, F., Ratib, O., Biomarkers, a.t.G.T.F.f.t.R.o.A.s. in this issue. Clinical validity of FDG-PET as a biomarker for Alzheimer's disease in the context of a structured 5-phase development framework. *Neurobiology of aging*.
- Hatashita, S., Yamasaki, H., Suzuki, Y., Tanaka, K., Wakebe, D., Hayakawa, H. 2014. [18F]Flutemetamol amyloid-beta PET imaging compared with [11C]PIB across the spectrum of Alzheimer's disease. *European journal of nuclear medicine and molecular imaging* 41(2), 290-300. doi:10.1007/s00259-013-2564-y.
- Heurling, K., Leuzy, A., Zimmer, E.R., Lubberink, M., Nordberg, A. 2016. Imaging beta-amyloid using [(18)F]flutemetamol positron emission tomography: from dosimetry to clinical diagnosis. *European journal of nuclear medicine and molecular imaging* 43(2), 362-73. doi:10.1007/s00259-015-3208-1.
- Hyman, B.T., Phelps, C.H., Beach, T.G., Bigio, E.H., Cairns, N.J., Carrillo, M.C., Dickson, D.W., Duyckaerts, C., Frosch, M.P., Masliah, E., Mirra, S.S., Nelson, P.T., Schneider, J.A., Thal, D.R., Thies, B., Trojanowski, J.Q., Vinters, H.V., Montine, T.J. 2012. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 8(1), 1-13. doi:10.1016/j.jalz.2011.10.007.
- Hyman, B.T., Trojanowski, J.Q. 1997. Editorial on consensus recommendations for the postmortem diagnosis of Alzheimer disease from the National Institute on Aging and the Reagan Institute working group on diagnostic criteria for the neuropathological assessment of Alzheimer disease. *Journal of neuropathology and experimental neurology* 56(10), 1095-7. doi:10.1097/00005072-199710000-00002.
- Ikonomic, M.D., Klunk, W.E., Abrahamson, E.E., Mathis, C.A., Price, J.C., Tsopelas, N.D., Lopresti, B.J., Ziolko, S., Bi, W., Paljug, W.R., Debnath, M.L., Hope, C.E., Isanski, B.A., Hamilton, R.L., DeKosky, S.T. 2008. Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. *Brain : a journal of neurology* 131(Pt 6), 1630-45. doi:10.1093/brain/awn016.
- Jack, C.R., Jr., Lowe, V.J., Senjem, M.L., Weigand, S.D., Kemp, B.J., Shiung, M.M., Knopman, D.S., Boeve, B.F., Klunk, W.E., Mathis, C.A., Petersen, R.C. 2008. 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnesic mild cognitive impairment. *Brain : a journal of neurology* 131(Pt 3), 665-80. doi:10.1093/brain/awn336.
- Jack, C.R., Jr., Wiste, H.J., Vemuri, P., Weigand, S.D., Senjem, M.L., Zeng, G., Bernstein, M.A., Gunter, J.L., Pankratz, V.S., Aisen, P.S., Weiner, M.W., Petersen, R.C., Shaw, L.M., Trojanowski, J.Q., Knopman, D.S., Alzheimer's Disease Neuroimaging, I. 2010. Brain beta-amyloid measures and magnetic resonance imaging atrophy both predict time-to-progression from mild cognitive impairment to Alzheimer's disease. *Brain : a journal of neurology* 133(11), 3336-48. doi:10.1093/brain/awq277.
- Jack, C.R., Jr., Wiste, H.J., Weigand, S.D., Rocca, W.A., Knopman, D.S., Mielke, M.M., Lowe, V.J., Senjem, M.L., Gunter, J.L., Preboske, G.M., Pankratz, V.S., Vemuri, P., Petersen, R.C. 2014. Age-specific population frequencies of cerebral beta-amyloidosis and neurodegeneration among people with normal cognitive function aged 50-89 years: a cross-sectional study. *The Lancet Neurology* 13(10), 997-1005. doi:10.1016/S1474-4422(14)70194-2.
- Jansen, W.J., Ossenkoppele, R., Knol, D.L., Tijms, B.M., Scheltens, P., Verhey, F.R.J., Visser, P.J., Grp, A.B.S. 2015. Prevalence of Cerebral Amyloid Pathology in Persons Without Dementia A Meta-analysis. *Jama-J Am Med Assoc* 313(19), 1924-38. doi:10.1001/jama.2015.4668.
- Johnson, K.A., Minoshima, S., Bohnen, N.I., Donohoe, K.J., Foster, N.L., Herscovitch, P., Karlawish, J.H., Rowe, C.C., Carrillo, M.C., Hartley, D.M., Hedrick, S., Pappas, V., Thies, W.H. 2013a. Appropriate use criteria for amyloid PET: a report of the Amyloid

Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* 54(3), 476-90. doi:10.2967/jnumed.113.120618.

Johnson, K.A., Sperling, R.A., Gidicsin, C.M., Carmasin, J.S., Maye, J.E., Coleman, R.E., Reiman, E.M., Sabbagh, M.N., Sadowsky, C.H., Fleisher, A.S., Murali Doraiswamy, P., Carpenter, A.P., Clark, C.M., Joshi, A.D., Lu, M., Grundman, M., Mintun, M.A., Pontecorvo, M.J., Skovronsky, D.M., group, A.A.s. 2013b. Flortetapir (F18-AV-45) PET to assess amyloid burden in Alzheimer's disease dementia, mild cognitive impairment, and normal aging. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 9(5 Suppl), S72-83. doi:10.1016/j.jalz.2012.10.007.

Joshi, A.D., Pontecorvo, M.J., Clark, C.M., Carpenter, A.P., Jennings, D.L., Sadowsky, C.H., Adler, L.P., Kovnat, K.D., Seibyl, J.P., Arora, A., Saha, K., Burns, J.D., Lowrey, M.J., Mintun, M.A., Skovronsky, D.M., Flortetapir, F.S.I. 2012. Performance characteristics of amyloid PET with flortetapir F 18 in patients with Alzheimer's disease and cognitively normal subjects. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* 53(3), 378-84. doi:10.2967/jnumed.111.090340.

Kadir, A., Marutle, A., Gonzalez, D., Scholl, M., Almkvist, O., Mousavi, M., Mustafiz, T., Darreh-Shori, T., Nennesmo, I., Nordberg, A. 2011. Positron emission tomography imaging and clinical progression in relation to molecular pathology in the first Pittsburgh Compound B positron emission tomography patient with Alzheimer's disease. *Brain : a journal of neurology* 134(Pt 1), 301-17. doi:10.1093/brain/awq349.

Kemppainen, N.M., Aalto, S., Karrasch, M., Nagren, K., Savisto, N., Oikonen, V., Viitanen, M., Parkkola, R., Rinne, J.O. 2008. Cognitive reserve hypothesis: Pittsburgh Compound B and fluorodeoxyglucose positron emission tomography in relation to education in mild Alzheimer's disease. *Annals of neurology* 63(1), 112-8. doi:10.1002/ana.21212.

Kemppainen, N.M., Scheinin, N.M., Koivunen, J., Johansson, J., Toivonen, J.T., Nagren, K., Rokka, J., Karrasch, M., Parkkola, R., Rinne, J.O. 2014. Five-year follow-up of 11C-PIB uptake in Alzheimer's disease and MCI. *European journal of nuclear medicine and molecular imaging* 41(2), 283-9. doi:10.1007/s00259-013-2562-0.

Klunk, W.E., Engler, H., Nordberg, A., Wang, Y., Blomqvist, G., Holt, D.P., Bergstrom, M., Savitcheva, I., Huang, G.F., Estrada, S., Ausen, B., Debnath, M.L., Barletta, J., Price, J.C., Sandell, J., Lopresti, B.J., Wall, A., Koivisto, P., Antoni, G., Mathis, C.A., Langstrom, B. 2004. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Annals of neurology* 55(3), 306-19. doi:10.1002/ana.20009.

Klunk, W.E., Koeppe, R.A., Price, J.C., Benzinger, T.L., Devous, M.D., Sr., Jagust, W.J., Johnson, K.A., Mathis, C.A., Minhas, D., Pontecorvo, M.J., Rowe, C.C., Skovronsky, D.M., Mintun, M.A. 2015. The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 11(1), 1-15 e1-4. doi:10.1016/j.jalz.2014.07.003.

Koivunen, J., Pirttila, T., Kemppainen, N., Aalto, S., Herukka, S.K., Jauhianen, A.M., Hanninen, T., Hallikainen, M., Nagren, K., Rinne, J.O., Soininen, H. 2008. PET amyloid ligand [11C]PIB uptake and cerebrospinal fluid beta-amyloid in mild cognitive impairment. *Dementia and geriatric cognitive disorders* 26(4), 378-83. doi:10.1159/000163927.

Koivunen, J., Scheinin, N., Virta, J.R., Aalto, S., Vahlberg, T., Nagren, K., Helin, S., Parkkola, R., Viitanen, M., Rinne, J.O. 2011. Amyloid PET imaging in patients with mild cognitive impairment: a 2-year follow-up study. *Neurology* 76(12), 1085-90. doi:10.1212/WNL.0b013e318212015e.

Landau, S.M., Breault, C., Joshi, A.D., Pontecorvo, M., Mathis, C.A., Jagust, W.J., Mintun, M.A., Alzheimer's Disease Neuroimaging, I. 2013a. Amyloid-beta imaging with Pittsburgh compound B and flortetapir: comparing radiotracers and quantification methods. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* 54(1), 70-7. doi:10.2967/jnumed.112.109009.

Landau, S.M., Lu, M., Joshi, A.D., Pontecorvo, M., Mintun, M.A., Trojanowski, J.Q., Shaw, L.M., Jagust, W.J., Alzheimer's Disease Neuroimaging, I. 2013b. Comparing positron emission tomography imaging and cerebrospinal fluid measurements of beta-amyloid. *Annals of neurology* 74(6), 826-36. doi:10.1002/ana.23908.

Landau, S.M., Marks, S.M., Mormino, E.C., Rabinovici, G.D., Oh, H., O'Neil, J.P., Wilson, R.S., Jagust, W.J. 2012a. Association of lifetime cognitive engagement and low beta-amyloid deposition. *Archives of neurology* 69(5), 623-29. doi:10.1001/archneurol.2011.2748.

Landau, S.M., Mintun, M.A., Joshi, A.D., Koeppe, R.A., Petersen, R.C., Aisen, P.S., Weiner, M.W., Jagust, W.J., Alzheimer's Disease Neuroimaging, I. 2012b. Amyloid deposition, hypometabolism, and longitudinal cognitive decline. *Annals of neurology* 72(4), 578-86. doi:10.1002/ana.23650.

Landau, S.M., Thomas, B.A., Thurfjell, L., Schmidt, M., Margolin, R., Mintun, M., Pontecorvo, M., Baker, S.L., Jagust, W.J., Alzheimer's Disease Neuroimaging, I. 2014. Amyloid PET imaging in Alzheimer's disease: a comparison of three radiotracers. *European journal of nuclear medicine and molecular imaging* 41(7), 1398-407. doi:10.1007/s00259-014-2753-3.

Lehmann, M., Ghosh, P.M., Madison, C., Karydas, A., Coppola, G., O'Neil, J.P., Huang, Y., Miller, B.L., Jagust, W.J., Rabinovici, G.D. 2014. Greater medial temporal hypometabolism and lower cortical amyloid burden in ApoE4-positive AD patients. *Journal of neurology, neurosurgery, and psychiatry* 85(3), 266-73. doi:10.1136/jnnp-2013-305858.

Leinonen, V., Rinne, J.O., Wong, D.F., Wolk, D.A., Trojanowski, J.Q., Sherwin, P.F., Smith, A., Heurling, K., Su, M., Grachev, I.D. 2014. Diagnostic effectiveness of quantitative [(1)(8)F]flutemetamol PET imaging for detection of fibrillar amyloid beta using cortical biopsy histopathology as the standard of truth in subjects with idiopathic normal pressure hydrocephalus. *Acta neuropathologica communications* 2, 46. doi:10.1186/2051-5960-2-46.

Leuzy, A., Carter, S.F., Chiotis, K., Almkvist, O., Wall, A., Nordberg, A. 2015. Concordance and Diagnostic Accuracy of [11C]PIB PET and Cerebrospinal Fluid Biomarkers in a Sample of Patients with Mild Cognitive Impairment and Alzheimer's Disease. *Journal of Alzheimer's disease : JAD* 45(4), 1077-88. doi:10.3233/JAD-142952.

Leuzy, A., Chiotis, K., Hasselbalch, S.G., Rinne, J.O., de Mendonça, A., Otto, M., Lleó, A., Castelo-Branco, M., Santana, I., Johansson, J., Anderl-Straub, S., von Arnim, C.A.F., Beer, A., Blesa, R., Fortea, J., S.K., H., Portelius, E., Pannee, J., Zetterberg, H., Blennow, K., Nordberg, A. 2016. Pittsburgh Compound-B imaging and cerebrospinal fluid amyloid-β in a multicentre European memory clinic study. *Brain : a journal of neurology* (in press).

Liu, Y., Zhu, L., Plossl, K., Choi, S.R., Qiao, H., Sun, X., Li, S., Zha, Z., Kung, H.F. 2010. Optimization of automated radiosynthesis of [18F]AV-45: a new PET imaging agent for Alzheimer's disease. *Nuclear medicine and biology* 37(8), 917-25. doi:10.1016/j.nucmedbio.2010.05.001.

Ma, Y., Zhang, S., Li, J., Zheng, D.M., Guo, Y., Feng, J., Ren, W.D. 2014. Predictive accuracy of amyloid imaging for progression from mild cognitive impairment to Alzheimer disease with different lengths of follow-up: a meta-analysis. [Corrected]. *Medicine* 93(27), e150. doi:10.1097/MD.0000000000000150.

Masters, C.L., Simms, G., Weinman, N.A., Multhaup, G., McDonald, B.L., Beyreuther, K. 1985. Amyloid plaque core protein in Alzheimer disease and Down syndrome. *Proceedings of the National Academy of Sciences of the United States of America* 82(12), 4245-9.

Mathis, C.A., Mason, N.S., Lopresti, B.J., Klunk, W.E. 2012. Development of positron emission tomography beta-amyloid plaque imaging agents. *Seminars in nuclear medicine* 42(6), 423-32. doi:10.1053/j.semnuclmed.2012.07.001.

Mathis, C.A., Wang, Y., Holt, D.P., Huang, G.F., Debnath, M.L., Klunk, W.E. 2003. Synthesis and evaluation of ¹¹C-labeled 6-substituted 2-arylbenzothiazoles as amyloid imaging agents. *Journal of medicinal chemistry* 46(13), 2740-54. doi:10.1021/jm030026b.

Mattsson, N., Insel, P.S., Landau, S., Jagust, W., Donohue, M., Shaw, L.M., Trojanowski, J.Q., Zetterberg, H., Blennow, K., Weiner, M., Alzheimer's Disease Neuroimaging, I. 2014. Diagnostic accuracy of CSF Aβ42 and florbetapir PET for Alzheimer's disease. *Annals of clinical and translational neurology* 1(8), 534-43. doi:10.1002/acn3.81.

Mattsson, N., Lönngberg, A., Boccardi, M., Blennow, K., Hansson, O., Biomarkers, a.t.G.T.F.f.t.R.o.A.s. in this issue. Clinical validity of Aβ42, tau, and phospho-tau in the cerebrospinal fluid as biomarkers for Alzheimer's disease in the context of a structured 5-phase development framework. *Neurobiology of aging*.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., Stadlan, E.M. 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 34(7), 939-44.

Mielke, M.M., Wiste, H.J., Weigand, S.D., Knopman, D.S., Lowe, V.J., Roberts, R.O., Geda, Y.E., Swenson-Dravis, D.M., Boeve, B.F., Senjem, M.L., Vemuri, P., Petersen, R.C., Jack, C.R., Jr. 2012. Indicators of amyloid burden in a population-based study of cognitively normal elderly. *Neurology* 79(15), 1570-7. doi:10.1212/WNL.0b013e31826e2696.

Mintun, M.A., Larossa, G.N., Sheline, Y.I., Dence, C.S., Lee, S.Y., Mach, R.H., Klunk, W.E., Mathis, C.A., DeKosky, S.T., Morris, J.C. 2006. [¹¹C]PIB in a nondemented population: potential antecedent marker of Alzheimer disease. *Neurology* 67(3), 446-52. doi:10.1212/01.wnl.0000228230.26044.a4.

Mirra, S.S., Heyman, A., McKeel, D., Sumi, S.M., Crain, B.J., Brownlee, L.M., Vogel, F.S., Hughes, J.P., van Belle, G., Berg, L. 1991. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology* 41(4), 479-86.

Mormino, E.C., Kluth, J.T., Madison, C.M., Rabinovici, G.D., Baker, S.L., Miller, B.L., Koeppe, R.A., Mathis, C.A., Weiner, M.W., Jagust, W.J., Alzheimer's Disease Neuroimaging, I. 2009. Episodic memory loss is related to hippocampal-mediated beta-amyloid deposition in elderly subjects. *Brain : a journal of neurology* 132(Pt 5), 1310-23. doi:10.1093/brain/awn320.

Morris, J.C., Blennow, K., Froelich, L., Nordberg, A., Soininen, H., Waldemar, G., Wahlund, L.O., Dubois, B. 2014. Harmonized diagnostic criteria for Alzheimer's disease: recommendations. *Journal of internal medicine* 275(3), 204-13. doi:10.1111/joim.12199.

Morris, J.C., Roe, C.M., Xiong, C., Fagan, A.M., Goate, A.M., Holtzman, D.M., Mintun, M.A. 2010. APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. *Annals of neurology* 67(1), 122-31. doi:10.1002/ana.21843.

Murphy, K.R., Landau, S.M., Choudhury, K.R., Hostage, C.A., Shpanskaya, K.S., Sair, H.I., Petrella, J.R., Wong, T.Z., Doraiswamy, P.M., Alzheimer's Disease Neuroimaging, I. 2013. Mapping the effects of ApoE4, age and cognitive status on ¹⁸F-florbetapir PET measured regional cortical patterns of beta-amyloid density and growth. *NeuroImage* 78, 474-80. doi:10.1016/j.neuroimage.2013.04.048.

Murray, M.E., Lowe, V.J., Graff-Radford, N.R., Liesinger, A.M., Cannon, A., Przybelski, S.A., Rawal, B., Parisi, J.E., Petersen, R.C., Kantarci, K., Ross, O.A., Duara, R., Knopman, D.S., Jack, C.R., Jr., Dickson, D.W. 2015. Clinicopathologic and ¹¹C-Pittsburgh compound B implications of Thal amyloid phase across the Alzheimer's disease spectrum. *Brain : a journal of neurology* 138(Pt 5), 1370-81. doi:10.1093/brain/awv050.

Nayate, A.P., Dubroff, J.G., Schmitt, J.E., Nasrallah, I., Kishore, R., Mankoff, D., Pryma, D.A., Initi, A.s.D.N. 2015. Use of Standardized Uptake Value Ratios Decreases Interreader Variability of [¹⁸F]Florbetapir PET Brain Scan Interpretation. *Am J Neuroradiol* 36(7), 1237-44. doi:10.3174/ajnr.A4281.

NCT01518374. Clinical Evaluation of Florbetapir F 18 (¹⁸F-AV-45). In: ClinicalTrialsgov [Internet] Bethesda (MD): National Library of Medicine (US) 2000-2016 Available from: <https://clinicaltrials.gov/show/NCT01518374>, Avid Radiopharmaceuticals.

NCT02353949. Investigating the Clinical Consequences of Flutemetamol-PET-scanning. In: ClinicalTrialsgov [Internet] Bethesda (MD): National Library of Medicine (US) 2000-2016 Available from: <https://clinicaltrials.gov/show/NCT02353949>, University of Zurich.

NCT02420756. Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) Study (IDEAS). In: ClinicalTrialsgov [Internet] Bethesda (MD): National Library of Medicine (US) 2000-2016 Available from: <https://clinicaltrials.gov/show/NCT02420756>, American College of Radiology Imaging Network.

NCT02681172. Impact of FBB PET Amyloid Imaging in Change of Diagnosis in Patients With AD. In: ClinicalTrialsgov [Internet] Bethesda (MD): National Library of Medicine (US) 2000-2016 Available from: <https://clinicaltrials.gov/show/NCT02681172>, Piramal Imaging Limited.

NCT02778971. Implications for Management of PET Amyloid Classification Technology (IMPACT). In: ClinicalTrialsgov [Internet] Bethesda (MD): National Library of Medicine (US) 2000-2016 Available from: <https://clinicaltrials.gov/show/NCT02778971>, University of Utah.

Nelissen, N., Van Laere, K., Thurfjell, L., Owenius, R., Vandenbulcke, M., Koole, M., Bormans, G., Brooks, D.J., Vandenberghe, R. 2009. Phase 1 study of the Pittsburgh compound B derivative ¹⁸F-flutemetamol in healthy volunteers and patients with probable Alzheimer disease. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* 50(8), 1251-9. doi:10.2967/jnumed.109.063305.

Ni, R., Gillberg, P.G., Bergfors, A., Marutle, A., Nordberg, A. 2013. Amyloid tracers detect multiple binding sites in Alzheimer's disease brain tissue. *Brain : a journal of neurology* 136(Pt 7), 2217-27. doi:10.1093/brain/awt142.

Nordberg, A., Carter, S.F., Rinne, J., Drzezga, A., Brooks, D.J., Vandenberghe, R., Perani, D., Forsberg, A., Langstrom, B., Scheinin, N., Karrasch, M., Nagren, K., Grimmer, T., Miederer, I., Edison, P., Okello, A., Van Laere, K., Nelissen, N., Vandenbulcke, M., Garibotto, V., Almkvist, O., Kalbe, E., Hinz, R., Herholz, K. 2013. A European multicentre PET study of fibrillar amyloid in Alzheimer's disease. *European journal of nuclear medicine and molecular imaging* 40(1), 104-14. doi:10.1007/s00259-012-2237-2.

Ong, K.T., Villemagne, V.L., Bahar-Fuchs, A., Lamb, F., Langdon, N., Catafau, A.M., Stephens, A.W., Seibyl, J., Dinkelborg, L.M., Reiningner, C.B., Putz, B., Rohde, B., Masters, C.L., Rowe, C.C. 2015. Abeta imaging with ¹⁸F-florbetaben in prodromal Alzheimer's disease: a prospective outcome study. *Journal of neurology, neurosurgery, and psychiatry* 86(4), 431-6. doi:10.1136/jnnp-2014-308094.

Ossenkoppele, R., Jansen, W.J., Rabinovici, G.D., Knol, D.L., van der Flier, W.M., van Berckel, B.N., Scheltens, P., Visser, P.J., Amyloid, P.E.T.S.G., Verfaillie, S.C., Zwan, M.D., Adriaanse, S.M., Lammertsma, A.A., Barkhof, F., Jagust, W.J., Miller, B.L., Rosen, H.J., Landau, S.M., Villemagne, V.L., Rowe, C.C., Lee, D.Y., Na, D.L., Seo, S.W., Sarazin, M., Roe, C.M., Sabri, O., Barthel, H., Koglin, N., Hodges, J., Leyton, C.E., Vandenberghe, R., van Laere, K., Drzezga, A., Forster, S., Grimmer, T., Sanchez-Juan, P., Carril, J.M., Mok, V., Camus, V., Klunk, W.E., Cohen, A.D., Meyer, P.T., Hellwig, S., Newberg, A., Frederiksen, K.S., Fleisher, A.S., Mintun, M.A., Wolk, D.A., Nordberg, A., Rinne, J.O., Chetelat, G., Lleo, A., Blesa, R., Fortea, J., Madsen, K., Rodrigue, K.M., Brooks, D.J. 2015. Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. *Jama* 313(19), 1939-49. doi:10.1001/jama.2015.4669.

Ossenkoppele, R., Prins, N.D., Pijnenburg, Y.A., Lemstra, A.W., van der Flier, W.M., Adriaanse, S.F., Windhorst, A.D., Handels, R.L., Wolfs, C.A., Aalten, P., Verhey, F.R., Verbeek, M.M., van Buchem, M.A., Hoekstra, O.S., Lammertsma, A.A., Scheltens, P., van Berckel, B.N. 2013a. Impact of molecular imaging on the diagnostic process in a memory clinic. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 9(4), 414-21. doi:10.1016/j.jalz.2012.07.003.

Ossenkoppele, R., van der Flier, W.M., Zwan, M.D., Adriaanse, S.F., Boellaard, R., Windhorst, A.D., Barkhof, F., Lammertsma, A.A., Scheltens, P., van Berckel, B.N. 2013b. Differential effect of APOE genotype on amyloid load and glucose metabolism in AD dementia. *Neurology* 80(4), 359-65. doi:10.1212/WNL.0b013e31827f0889.

Payoux, P., Delrieu, J., Gallini, A., Adel, D., Salabert, A.S., Hitzel, A., Cantet, C., Tafani, M., De Verbizier, D., Darcourt, J., Fernandez, P., Monteil, J., Carrie, I., Voisin, T., Gillette-Guyonnet, S., Pontecorvo, M., Vellas, B., Andrieu, S. 2015. Cognitive and functional patterns of nondemented subjects with equivocal visual amyloid PET findings. *European journal of nuclear medicine and molecular imaging* 42(9), 1459-68. doi:10.1007/s00259-015-3067-9.

Pepe, M.S., Etzioni, R., Feng, Z., Potter, J.D., Thompson, M.L., Thornequist, M., Winget, M., Yasui, Y. 2001. Phases of biomarker development for early detection of cancer. *Journal of the National Cancer Institute* 93(14), 1054-61.

Price, J.C., Klunk, W.E., Lopresti, B.J., Lu, X., Hoge, J.A., Ziolkowski, S.K., Holt, D.P., Meltzer, C.C., DeKosky, S.T., Mathis, C.A. 2005. Kinetic modeling of amyloid binding in humans using PET imaging and Pittsburgh Compound-B. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism* 25(11), 1528-47. doi:10.1038/sj.jcbfm.9600146.

Rabinovici, G.D., Furst, A.J., Alkalay, A., Racine, C.A., O'Neil, J.P., Janabi, M., Baker, S.L., Agarwal, N., Bonasera, S.J., Mormino, E.C., Weiner, M.W., Gorno-Tempini, M.L., Rosen, H.J., Miller, B.L., Jagust, W.J. 2010. Increased metabolic vulnerability in early-onset Alzheimer's disease is not related to amyloid burden. *Brain : a journal of neurology* 133(Pt 2), 512-28. doi:10.1093/brain/awp326.

Rabinovici, G.D., Rosen, H.J., Alkalay, A., Kornak, J., Furst, A.J., Agarwal, N., Mormino, E.C., O'Neil, J.P., Janabi, M., Karydas, A., Growdon, M.E., Jang, J.Y., Huang, E.J., Dearmond, S.J., Trojanowski, J.Q., Grinberg, L.T., Gorno-Tempini, M.L., Seeley, W.W., Miller, B.L., Jagust, W.J. 2011. Amyloid vs FDG-PET in the differential diagnosis of AD and FTLD. *Neurology* 77(23), 2034-42. doi:10.1212/WNL.0b013e31823b9c5e.

Reiman, E.M., Chen, K., Liu, X., Bandy, D., Yu, M., Lee, W., Ayutyanont, N., Keppler, J., Reeder, S.A., Langbaum, J.B., Alexander, G.E., Klunk, W.E., Mathis, C.A., Price, J.C., Aizenstein, H.J., DeKosky, S.T., Caselli, R.J. 2009. Fibrillar amyloid-beta burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America* 106(16), 6820-5. doi:10.1073/pnas.0900345106.

Rinne, J.O., Wong, D.F., Wolk, D.A., Leinonen, V., Arnold, S.E., Buckley, C., Smith, A., McLain, R., Sherwin, P.F., Farrar, G., Kailajarvi, M., Grachev, I.D. 2012. [(18)F]Flutemetamol PET imaging and cortical biopsy histopathology for fibrillar amyloid beta detection in living subjects with normal pressure hydrocephalus: pooled analysis of four studies. *Acta neuropathologica* 124(6), 833-45. doi:10.1007/s00401-012-1051-z.

Rowe, C.C., Ackerman, U., Browne, W., Mulligan, R., Pike, K.L., O'Keefe, G., Tochon-Danguy, H., Chan, G., Berlangieri, S.U., Jones, G., Dickinson-Rowe, K.L., Kung, H.P., Zhang, W., Kung, M.P., Skovronsky, D., Dyrks, T., Holl, G., Krause, S., Friebe, M., Lehman, L., Lindemann, S., Dinkelborg, L.M., Masters, C.L., Villemagne, V.L. 2008. Imaging of amyloid beta in Alzheimer's disease with 18F-BAY94-9172, a novel PET tracer: proof of mechanism. *The Lancet Neurology* 7(2), 129-35. doi:10.1016/S1474-4422(08)70001-2.

Rowe, C.C., Bourgeat, P., Ellis, K.A., Brown, B., Lim, Y.Y., Mulligan, R., Jones, G., Maruff, P., Woodward, M., Price, R., Robins, P., Tochon-Danguy, H., O'Keefe, G., Pike, K.E., Yates, P., Szoek, C., Salvado, O., Macaulay, S.L., O'Meara, T., Head, R., Cobiac, L., Savage, G., Martins, R., Masters, C.L., Ames, D., Villemagne, V.L. 2013a. Predicting Alzheimer disease with beta-amyloid imaging: results from the Australian imaging, biomarkers, and lifestyle study of ageing. *Annals of neurology* 74(6), 905-13. doi:10.1002/ana.24040.

Rowe, C.C., Ellis, K.A., Rimajova, M., Bourgeat, P., Pike, K.E., Jones, G., Fripp, J., Tochon-Danguy, H., Morandau, L., O'Keefe, G., Price, R., Raniga, P., Robins, P., Acosta, O., Lenzo, N., Szoek, C., Salvado, O., Head, R., Martins, R., Masters, C.L., Ames, D., Villemagne, V.L. 2010. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. *Neurobiology of aging* 31(8), 1275-83. doi:10.1016/j.neurobiolaging.2010.04.007.

Rowe, C.C., Pejoska, S., Mulligan, R.S., Jones, G., Chan, J.G., Svensson, S., Cselenyi, Z., Masters, C.L., Villemagne, V.L. 2013b. Head-to-head comparison of 11C-PiB and 18F-AZD4694 (NAV4694) for beta-amyloid imaging in aging and dementia. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* 54(6), 880-6. doi:10.2967/jnumed.112.114785.

Rowe, C.C., Pejoska, S., Mulligan, R.S. 2009. Test-retest variability of high and low specific activity [18F]BAY 94-9172 in Alzheimer's disease and normal ageing. *Society of Nuclear Medicine meeting, Toronto, Canada*, pp Abstract #1252.

Sabri, O., Sabbagh, M.N., Seibyl, J., Barthel, H., Akatsu, H., Ouchi, Y., Senda, K., Murayama, S., Ishii, K., Takao, M., Beach, T.G., Rowe, C.C., Leverenz, J.B., Ghetti, B., Ironside, J.W., Catafau, A.M., Stephens, A.W., Mueller, A., Koglin, N., Hoffmann, A., Roth, K., Reininger, C., Schulz-Schaeffer, W.J., Florbetaben Phase 3 Study, G. 2015. Florbetaben PET imaging to detect amyloid beta plaques in Alzheimer's disease: Phase 3 study. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 11(8), 964-74. doi:10.1016/j.jalz.2015.02.004.

Saint-Aubert, L., Nemmi, F., Peran, P., Barbeau, E.J., Payoux, P., Chollet, F., Pariente, J. 2014. Comparison between PET template-based method and MRI-based method for cortical quantification of florbetapir (AV-45) uptake in vivo. *European journal of nuclear medicine and molecular imaging* 41(5), 836-43. doi:10.1007/s00259-013-2656-8.

Sanchez-Juan, P., Ghosh, P.M., Hagen, J., Gesierich, B., Henry, M., Grinberg, L.T., O'Neil, J.P., Janabi, M., Huang, E.J., Trojanowski, J.Q., Vinters, H.V., Gorno-Tempini, M., Seeley, W.W., Boxer, A.L., Rosen, H.J., Kramer, J.H., Miller, B.L., Jagust, W.J., Rabinovici, G.D. 2014. Practical utility of amyloid and FDG-PET in an academic dementia center. *Neurology* 82(3), 230-8. doi:10.1212/WNL.000000000000032.

- Scheinin, N.M., Wikman, K., Jula, A., Perola, M., Vahlberg, T., Rokka, J., Nagren, K., Viitanen, M., Rinne, J.O. 2014. Cortical (1)(1)C-PIB uptake is associated with age, APOE genotype, and gender in "healthy aging". *Journal of Alzheimer's disease : JAD* 41(1), 193-202. doi:10.3233/JAD-132783.
- Schreiber, S., Landau, S.M., Fero, A., Schreiber, F., Jagust, W.J., Alzheimer's Disease Neuroimaging, I. 2015. Comparison of Visual and Quantitative Florbetapir F 18 Positron Emission Tomography Analysis in Predicting Mild Cognitive Impairment Outcomes. *JAMA neurology*. doi:10.1001/jamaneurol.2015.1633.
- Shoghi-Jadid, K., Small, G.W., Agdeppa, E.D., Kepe, V., Ercoli, L.M., Siddarth, P., Read, S., Satyamurthy, N., Petric, A., Huang, S.C., Barrio, J.R. 2002. Localization of neurofibrillary tangles and beta-amyloid plaques in the brains of living patients with Alzheimer disease. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry* 10(1), 24-35.
- Small, G.W., Kepe, V., Ercoli, L.M., Siddarth, P., Bookheimer, S.Y., Miller, K.J., Lavretsky, H., Burggren, A.C., Cole, G.M., Vinters, H.V., Thompson, P.M., Huang, S.C., Satyamurthy, N., Phelps, M.E., Barrio, J.R. 2006. PET of brain amyloid and tau in mild cognitive impairment. *The New England journal of medicine* 355(25), 2652-63. doi:10.1056/NEJMoa054625.
- Smid, L.M., Vovko, T.D., Popovic, M., Petric, A., Kepe, V., Barrio, J.R., Vidmar, G., Bresjanac, M. 2006. The 2,6-disubstituted naphthalene derivative FDDNP labeling reliably predicts Congo red birefringence of protein deposits in brain sections of selected human neurodegenerative diseases. *Brain pathology* 16(2), 124-30. doi:10.1111/j.1750-3639.2006.00006.x.
- Sonni, I., Ratib, O., Boccardi, M., Picco, A., Herholz, K., Nobili, F., Varrone, A., Biomarkers, a.t.G.T.f.t.R.o.A.s. in this issue. Clinical validity of presynaptic dopaminergic imaging with 123I-ioflupane and noradrenergic imaging with 123I-MIBG SPECT in the differential diagnosis between Alzheimer's disease and Dementia with Lewy bodies in the context of a structured 5-phase development framework. *Neurobiology of aging*.
- Ten Kate, M., Barkhof, F., Boccardi, M., Visser, P.J., Lovblad, K.O., Jack, C.R., Frisoni, G.B., Scheltens, P., Biomarkers, a.t.G.T.f.t.R.o.A.s. in this issue. Clinical validity of medial temporal atrophy as a biomarker for Alzheimer's disease in the context of a structured 5-phase development framework. *Neurobiology of aging*.
- Thal, D.R., Beach, T.G., Zanning, M., Heurling, K., Chakrabarty, A., Ismail, A., Smith, A.P., Buckley, C. 2015. [(18)F]flutemetamol amyloid positron emission tomography in preclinical and symptomatic Alzheimer's disease: Specific detection of advanced phases of amyloid-beta pathology. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 11(8), 975-85. doi:10.1016/j.jalz.2015.05.018.
- Thal, D.R., Rub, U., Orantes, M., Braak, H. 2002. Phases of A beta-deposition in the human brain and its relevance for the development of AD. *Neurology* 58(12), 1791-800.
- Thurfjell, L., Lilja, J., Lundqvist, R., Buckley, C., Smith, A., Vandenberghe, R., Sherwin, P. 2014. Automated quantification of 18F-flutemetamol PET activity for categorizing scans as negative or positive for brain amyloid: concordance with visual image reads. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* 55(10), 1623-8. doi:10.2967/jnumed.114.142109.
- Thurfjell, L., Lotjonen, J., Lundqvist, R., Koikkalainen, J., Soininen, H., Waldemar, G., Brooks, D.J., Vandenberghe, R. 2012. Combination of biomarkers: PET [18F]flutemetamol imaging and structural MRI in dementia and mild cognitive impairment. *Neurodegenerative diseases* 10(1-4), 246-9. doi:10.1159/000335381.
- Trzepacz, P.T., Yu, P., Sun, J., Schuh, K., Case, M., Witte, M.M., Hochstetler, H., Hake, A., Alzheimer's Disease Neuroimaging, I. 2014. Comparison of neuroimaging modalities for the prediction of conversion from mild cognitive impairment to Alzheimer's dementia. *Neurobiology of aging* 35(1), 143-51. doi:10.1016/j.neurobiolaging.2013.06.018.
- Vandenberghe, R., Nelissen, N., Salmon, E., Ivanoiu, A., Hasselbalch, S., Andersen, A., Korner, A., Minthon, L., Brooks, D.J., Van Laere, K., Dupont, P. 2013. Binary classification of (1)(8)F-flutemetamol PET using machine learning: comparison with visual reads and structural MRI. *NeuroImage* 64, 517-25. doi:10.1016/j.neuroimage.2012.09.015.
- Vandenberghe, R., Van Laere, K., Ivanoiu, A., Salmon, E., Bastin, C., Triau, E., Hasselbalch, S., Law, I., Andersen, A., Korner, A., Minthon, L., Garraux, G., Nelissen, N., Bormans, G., Buckley, C., Owenius, R., Thurfjell, L., Farrar, G., Brooks, D.J. 2010. 18F-flutemetamol amyloid imaging in Alzheimer disease and mild cognitive impairment: a phase 2 trial. *Annals of neurology* 68(3), 319-29. doi:10.1002/ana.22068.
- Villemagne, V.L., Mulligan, R.S., Pejoska, S., Ong, K., Jones, G., O'Keefe, G., Chan, J.G., Young, K., Tochon-Danguy, H., Masters, C.L., Rowe, C.C. 2012. Comparison of 11C-PiB and 18F-florbetaben for Abeta imaging in ageing and Alzheimer's disease. *European journal of nuclear medicine and molecular imaging* 39(6), 983-9. doi:10.1007/s00259-012-2088-x.
- Villemagne, V.L., Ong, K., Mulligan, R.S., Holl, G., Pejoska, S., Jones, G., O'Keefe, G., Ackerman, U., Tochon-Danguy, H., Chan, J.G., Reininger, C.B., Fels, L., Putz, B., Rohde, B., Masters, C.L., Rowe, C.C. 2011a. Amyloid imaging with (18)F-florbetaben in Alzheimer disease and other dementias. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* 52(8), 1210-7. doi:10.2967/jnumed.111.089730.
- Villemagne, V.L., Pike, K.E., Chetelat, G., Ellis, K.A., Mulligan, R.S., Bourgeat, P., Ackermann, U., Jones, G., Szeoke, C., Salvado, O., Martins, R., O'Keefe, G., Mathis, C.A., Klunk, W.E., Ames, D., Masters, C.L., Rowe, C.C. 2011b. Longitudinal assessment of Abeta and cognition in aging and Alzheimer disease. *Annals of neurology* 69(1), 181-92. doi:10.1002/ana.22248.
- Villeneuve, S., Rabinovici, G.D., Cohn-Sheehy, B.I., Madison, C., Ayakta, N., Ghosh, P.M., La Joie, R., Arthur-Bentil, S.K., Vogel, J.W., Marks, S.M., Lehmann, M., Rosen, H.J., Reed, B., Olichney, J., Boxer, A.L., Miller, B.L., Borys, E., Jin, L.W., Huang, E.J., Grinberg, L.T., DeCarli, C., Seeley, W.W., Jagust, W. 2015a. Existing Pittsburgh Compound-B positron emission tomography thresholds are too high: statistical and pathological evaluation. *Brain : a journal of neurology* 138(Pt 7), 2020-33. doi:10.1093/brain/awv112.
- Villeneuve, S., St. Amant, H., Vogel, J.W., Marks, S., Wirth, M., DeCarli, C., Jagust, W.J. 2015b. Are low levels of PIB-PET signal clinically significant? Alzheimer's Association International Conference. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, Washington, D.C., U.S.A.
- Wirth, M., Villeneuve, S., La Joie, R., Marks, S.M., Jagust, W.J. 2014. Gene-environment interactions: lifetime cognitive activity, APOE genotype, and beta-amyloid burden. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 34(25), 8612-7. doi:10.1523/JNEUROSCI.4612-13.2014.
- Wolk, D.A., Grachev, I.D., Buckley, C., Kazi, H., Grady, M.S., Trojanowski, J.Q., Hamilton, R.H., Sherwin, P., McLain, R., Arnold, S.E. 2011. Association between in vivo fluorine 18-labeled flutemetamol amyloid positron emission tomography imaging and in vivo cerebral cortical histopathology. *Archives of neurology* 68(11), 1398-403. doi:10.1001/archneurol.2011.153.
- Wolk, D.A., Zhang, Z., Boudhar, S., Clark, C.M., Pontecorvo, M.J., Arnold, S.E. 2012. Amyloid imaging in Alzheimer's disease: comparison of florbetapir and Pittsburgh compound-B positron emission tomography. *Journal of neurology, neurosurgery, and psychiatry* 83(9), 923-6. doi:10.1136/jnnp-2012-302548.

Wong, D.F., Rosenberg, P.B., Zhou, Y., Kumar, A., Raymont, V., Ravert, H.T., Dannals, R.F., Nandi, A., Brasic, J.R., Ye, W., Hilton, J., Lyketsos, C., Kung, H.F., Joshi, A.D., Skovronsky, D.M., Pontecorvo, M.J. 2010. In vivo imaging of amyloid deposition in Alzheimer disease using the radioligand 18F-AV-45 (florbetapir [corrected] F 18). *Journal of nuclear medicine : official publication, Society of Nuclear Medicine* 51(6), 913-20. doi:10.2967/jnumed.109.069088.

Yasuno, F., Kazui, H., Morita, N., Kajimoto, K., Ihara, M., Taguchi, A., Yamamoto, A., Matsuoka, K., Kosaka, J., Kudo, T., Iida, H., Kishimoto, T. 2014. Low amyloid-beta deposition correlates with high education in cognitively normal older adults: a pilot study. *International journal of geriatric psychiatry*. doi:10.1002/gps.4235.

Yeo, J.M., Waddell, B., Khan, Z., Pal, S. 2015. A systematic review and meta-analysis of (18)F-labeled amyloid imaging in Alzheimer's disease. *Alzheimer's & dementia* 1(1), 5-13. doi:10.1016/j.dadm.2014.11.004.