Clinical validity of increased cortical uptake of [^{18}F]flortaucipir on PET as a biomarker for Alzheimer's disease in the context of a structured 5-phase biomarker development framework

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Abstract

Purpose:

In 2017, the Geneva Alzheimer's disease (AD) Biomarker Roadmap Initiative adapted the framework of the systematic validation of oncological diagnostic biomarkers to AD biomarkers, with the aim to accelerate their development and implementation in clinical practice. With this work we assess the maturity of [^{18}F]flortaucipir PET and define its research priorities.

Methods: The level of maturity of [^{18}F]flortaucipir was assessed based on the AD Biomarker Roadmap. The framework assesses Analytical Validity (Phases 1-2), Clinical Validity (Phases 3-4) and Clinical Utility (Phase 5).

Results: The main aims of phase 1 (rationale for use) and 2 (discriminative ability) have been achieved. [^{18}F]Flortaucipir binds with high affinity to paired helical filaments of tau, has favorable kinetic properties and excellent discriminative accuracy for AD. The majority of secondary aims of phase 2 were fully achieved. Multiple studies showed high correlations between ante-mortem [^{18}F]flortaucipir PET and post-mortem tau (as assessed by histopathology) and also the effects of covariates on tracer binding are well-studied. The aims of phase 3 (early detection ability) were only partially or preliminary achieved, and the aims of phase 4 and 5 were not achieved.

Conclusion:

Current literature provides partial evidence for clinical utility of [^{18}F]flortaucipir PET. The aims for phase 1 and 2 were mostly achieved. Phase 3 studies are currently ongoing. Future studies including representative MCI populations and a focus on health care outcomes are required to establish full maturity of phase 4 and 5.

Keywords: Alzheimer's Disease, strategic roadmap, biomarker-based diagnosis, [^{18}F]flortaucipir, PET

1. Introduction

In 2017, a methodological framework for the systematic assessment of biomarker validation was imported from oncology (Pepe, Etzioni et al. 2001) and adapted to Alzheimer's disease (AD) (Boccardi, Gallo et al. 2017). This framework assesses Analytical Validity (Phases 1-2), Clinical Validity (Phases 3-4) and Clinical Utility (Phase 5) in steps to be fulfilled sequentially to prevent conveying uncontrollable variability in downstream validation studies (Fig-1). Within this "Biomarker Roadmap" initiative, we assessed the validation status of consolidated AD-biomarkers at that time (Frisoni, Boccardi et al. 2017): episodic memory (Cerami, Dubois et al. 2017), cerebrospinal fluid (CSF) (Mattsson, Lonneborg et al. 2017), medial temporal atrophy (Ten Kate, Barkhof et al. 2017), FDG-PET (Garibotto, Herholz et al. 2017), amyloid PET (Chiotis, Saint-Aubert et al. 2017) and 123I-ioflupane brain single photon emission tomography and 123I-MIBG cardiac scintigraphy (Sonni, Ratib et al. 2017).

The aim of this work is to assess the validation status of the tau PET tracer [^{18}F]flortaucipir based on the Biomarker Roadmap methodology. Tau-PET has been recently introduced among the T biomarkers in the AT(N) research framework (A = Amyloid-β, T = Tau, N = Neurodegeneration (Jack, Bennett et al. 2018)). Despite the promising preliminary results in the last few years, its maturity for standard use in clinical practice has yet to be defined. We now have developed a methodological framework to assess biomarkers of brain tauopathy (Boccardi, Dodich et al. 2020).

The first generation tau tracer [^{18}F]flortaucipir was first described in 2013 (Chien, Bahri et al. 2013, Xia, Arteaga et al. 2013) and is currently the most widely used tau PET tracer worldwide. [^{18}F]Flortaucipir binds predominantly to paired helical filaments (PHFs) typically observed in AD (Xia, Arteaga et al. 2013, Marquie, Normandin et al. 2015, Lowe, Curran et al. 2016, Fleisher, Pontecorvo et al. 2020) and was recently approved by the U.S. Food and Drug Administration for detection of aggregated tau pathology by visual read in persons with suspected AD dementia (FDA 2020). This review systematically investigates [^{18}F]flortaucipir PET studies in order to assess the validation maturity of [^{18}F]flortaucipir PET and to define its clinical validity for the diagnosis of (prodromal) AD.

2. Methods

2.1. Target

This literature review investigates the validation status of tau-PET with [^{18}F]flortaucipir as biomarker of neurodegenerative disorders possibly due to AD, in accordance with the 2017 Biomarker Roadmap (Boccardi, Gallo et al. 2017, Frisoni, Boccardi et al. 2017) and its updates (Boccardi, Dodich et al.

2020).The target population consists of patients with mild cognitive impairment (MCI) referring to memory clinics for ascertained cognitive complaints, attributed to possible sporadic and not familial neurodegenerative disorders leading to dementia. Validation studies of [^{18}F]flortaucipir were eligible for this review when including AD neuropathology, *in vivo* amyloid status as determined by AD-biomarkers, or development of incidental AD dementia after two-years of follow up as reference standard for the biomarker-based diagnosis. Thus, eligible studies included both prospective longitudinal and cross-sectional studies. This review will only assess the evidence available for [^{18}F]flortaucipir. Other tau PET tracers (in this issue) and tau biofluid markers (in this issue) will be discussed elsewhere.

2.2. Glossary

2.2.1. Alzheimer's disease

By Alzheimer's disease we refer to the presence of extracellular amyloid-β plaques and aggregates of hyper-phosphorylated tau in neurofibrillary tangles. These features define AD independently of the clinical expression of cognitive symptoms.

2.2.2. AD dementia

AD dementia denotes an acquired and progressive cognitive and functional loss of autonomy, according to previous criteria as defined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann, Drachman et al. 1984). Notably, because of the imperfect accuracy of purely clinical criteria, a percentage of AD dementia cases might have underlying non-AD pathology.

2.2.3. Mild cognitive impairment

This refers to a condition within the AD population without functional disability, but with an acquired objective cognitive impairment. Representing a clinical syndrome, it encompasses cases progressing to AD (~50%) or non-AD dementia (about 10%-15%; (Bennett, Wilson et al. 2002, Jack, Lowe et al. 2008, Rowe, Ellis et al. 2010) as well as stable cases (about 35%-40%). MCI cases positive to AD biomarkers have been defined as "prodromal AD" following previous guidelines (Dubois, Feldman et al. 2014). The diagnosis of AD at the MCI stage represents the focus of the AD Biomarker Roadmap.

2.2.3. Non-AD neurodegenerative disease

This term refers to all neurodegenerative disorders considered for the differential diagnosis, including a large pathological spectrum (hippocampal sclerosis, limbic-predominant age-related TDP-43, frontotemporal lobar degeneration (FTLD), Lewy body dementia (LBD), chronic traumatic encephalopathy, multiple system atrophy, and so forth).

2.3 Conceptual framework

The conceptual framework is described in detail (Boccardi, Gallo et al. 2017). The phases and fulfillment of aims were initially developed in oncology (Pepe, Etzioni et al. 2001), adapted to AD (Boccardi, Gallo et al. 2017) and recently updated (Boccardi, Dodich et al. 2020). This conceptual framework allows for systematic assessment of analytical validity (Phases 1-2), clinical validity (Phases 3-4) and clinical utility (Phase 5) through Primary and Secondary Aims. Analytical validity (i.e., accuracy) of [^{18}F]flortaucipir is demonstrated with respect to the gold standard (neuropathology) and is also present when the assay provides measurements with sufficient precision (i.e., reliability), that are consistent over time and in different contexts or circumstances. The clinical validity of [^{18}F]flortaucipir is the ability to detect the presence of a sign that is clearly separate from normal controls, and from "adjacent" signs (or proxies for diseases) on the other hand. Once the biomarker-disease association is established and understood, standard tests to determine the customary validity measures (i.e., sensitivity and specificity) should be conducted to formally explore how the test performs in practice. The clinical utility of [^{18}F]flortaucipir is a function of the clinical implications of the results. The purpose of the test is of paramount importance to establish its clinical utility, which can potentially be achieved even though the disease (i.e., MCI due to AD) is not yet fully understood (Boccardi, Gallo et al. 2017, Boccardi, Dodich et al. 2020) .

For each phase/aim, different strings were used to detect relevant studies, which were selected following PRISMA guidelines (see online resource for strings and PRISMA results). For all included studies, relevant information about study design, methods and results were recorded.

2.3.1. Phase 1

This phase assesses analytical validity and includes preclinical exploratory studies on the rational for using [^{18}F]flortaucipir for diagnostic purposes for AD. The gold-standard for Phase 1 studies is neuropathology.

2.3.2. Phase 2

Phase-2 studies, still entailing analytical validity, investigate the diagnostic accuracy of [^{18}F]flortaucipir to distinguish patients with AD dementia from controls. Phase-2 studies are meant to define the clinical assay to allow reliable assessment, and identify the effect of confounders on the level of biomarker that may affect the threshold for positivity in both patients and controls (e.g., age, gender, apolipoprotein ε4 (APOE ε4) status, education or comorbidities).

2.3.3. Phase 3

Phase-3 studies assess clinical validity, i.e., the ability of the biomarker to detect the disease at its earliest possible phase, namely MCI for this specific effort, in well-controlled experimental samples. Phase-3 studies aim to define criteria for positivity, to compare the diagnostic performance with other

biomarkers, and to assess the diagnostic value of combinations of biomarkers, in view of defining a biomarker-based algorithm.

2.3.4. Phase 4

Phase-4 studies assess the clinical validity of [^{18}F]flortaucipir in representative patient cohorts from memory clinics. The biomarker itself is used to deliver a clinical diagnosis to patients with MCI who are subsequently treated based on this biomarker-based diagnosis. They are meant to ascertain clinical validity in patients with comorbidities and less strictly controlled conditions, and to start quantify the benefit of biomarker-based early detection, practical feasibility, protocol compliance and costs to prepare Phase 5.

2.3.5. Phase 5

Phase-5 studies quantify the clinical utility of [^{18}F]flortaucipir-based diagnosis in terms of impact on society (e.g, cost-effectiveness relative to clinically meaningful outcomes).

2.4. Assessment of Aim compliance

The fulfillment of each validation step from Phase-1 to Phase-5 has been assessed consistently with the 2017 Biomarker Roadmap and the methodological update (Boccardi, Gallo et al. 2017, Boccardi, Dodich et al. 2020). However, in this initiative we have performed a data extraction that summarizes the available data, thus allowing the reader to make its own appraisal of Aim compliance, and preparing to sounder evidence assessment. To that end, for each Primary and Secondary Aim of each study we have extracted data consistent with formal evidence assessment as previously described (Boccardi, Festari et al. 2018). Tables with data extraction are accessible online (https://drive.switch.ch/index.php/s/4reUTSuqNZHyIC8).

Potential outcomes for each aim include:

1. Fully achieved: available scientific evidence, successfully replicated in properly powered and well-designed studies.
2. Partly achieved: the available evidence is not sufficiently replicated, or samples are not adequately powered, or studies are faulted with major methodological limitations.
3. Preliminary evidence: only preliminary evidence is available.
4. Not achieved: studies are not yet performed at the time of the review.
5. Unsuccessful: Available scientific evidence shows a failure for the biomarker in achieving the aim. Findings in the subsequent roadmap phases should be interpreted with caution.

2.5. Manuscript search and selection

PubMed and Embase® were searched for relevant studies. The search was conducted on 05.05.2020 by author EW and replicated by author JC.
The keywords used to identify articles about [^{18}F]flortaucipir (formerly known as AV1451 or T807) PET imaging are reported in supplementary table 1.

We first screened the title and abstract of the papers, added papers from other sources (personal knowledge, references from these or other papers) and then excluded redundancies. The reasons for exclusion and the number of finally retained papers are reported according to the PRISMA guidance. Details for each phase/aim are available on online resource.

Results

3. Current clinical validity of tau-PET imaging
    3.1. Phase 1. Preclinical exploratory studies
        3.1.1.Primary aim: To identify and prioritize leads for potentially useful biomarkers.

Neurofibrillary tau tangles are one of the main pathological hallmarks of AD (Grundke-Iqbal, Iqbal et al. 1986, Braak and Braak 1991, Hyman, Phelps et al. 2012). [^{18}F]flortaucipir binds to paired helical filaments (PHFs) of tau with an 25 fold higher affinity than for amyloid-β in AD patients (Chien, Bahri et al. 2013, Xia, Arteaga et al. 2013, Marquie, Normandin et al. 2015, Lowe, Curran et al. 2016). However, the tracer is also characterized by off-target binding in the basal ganglia, thalamus and choroid plexus (Marquie, Normandin et al. 2015, Lowe, Curran et al. 2016). The *in vivo* kinetics of [^{18}F]flortaucipir are described as favorable, with rapid clearance from plasma and polar metabolites not entering the brain (Baker, Lockhart et al. 2017, Barret, Alagille et al. 2017, Golla, Timmers et al. 2017, Hahn, Schain et al. 2017, Wooten, Guehl et al. 2017). This aim was considered fully achieved (Fig-1).

    3.2. Phase 2. Clinical assay development for clinical Alzheimer's disease
        3.2.1. Phase 2. Primary aim: To estimate true positive and false positive rates, or receiving operating characteristics curves (ROC) for the essay and to identify the discrimination accuracy between subjects with and without the disease.

To date, one multi-center study comprising 719 participants assessed the diagnostic accuracy of [^{18}F]flortaucipir PET in distinguishing AD from non-AD neurodegenerative disorders (Ossenkoppele, Rabinovici et al. 2018). The gold standard was a clinical diagnosis of AD supported by amyloid-β positive biomarkers. The area under the curves (AUCs) of [^{18}F]flortaucipir uptake in the medial basal and lateral temporal cortex were 0.94-0.98, depending on the cut-off methods used for distinguishing AD dementia from non-AD neurodegenerative disorders. Similar results were found in another study (Jack, Wiste et al. 2019). The discriminative accuracy was lower for MCI due to AD vs. non-AD neurodegenerative

diseases with an AUC of 0.82 (Ossenkoppele, Rabinovici et al. 2018). In a secondary analysis, the diagnostic performance of [^{18}F]flortaucipir PET in distinguishing MCI due to AD (AUC 0.86) / AD dementia (AUC 0.97) vs. controls was examined. In addition, two other studies investigated the diagnostic performance of [^{18}F]flortaucipir PET in a clinical sample, which consisted of both AD and non-AD neurodegenerative disorders (La Joie, Bejanin et al. 2018) and prodromal / AD dementia and controls (Mattsson, Smith et al. 2018, Mattsson, Insel et al. 2019). However, both cohorts included overlapping samples with the earlier described larger multi-center study (Ossenkoppele, Rabinovici et al. 2018), therefore, we do not consider these results independent. Another study assessed partly a new cohort in ADNI, consisting of MCI/AD patients and Aβ- older controls. The diagnostic performance of [^{18}F]flortaucipir for distinguishing MCI/AD from controls was overall lower compared to previous study (Ossenkoppele, Rabinovici et al. 2018) with AUCs values between 0.76 and 0.87 (Maass, Landau et al. 2017). In addition, when [^{18}F]flortaucipir hippocampal and AD cortical signature regions were used for distinguishing AD from controls, AUCs of 0.89 to 0.98 were found, respectively (Wang, Benzinger et al. 2016). This aim was considered fully achieved (Fig-1).

3.2.2. Phase 2. Secondary aim 1: To optimize procedures for performing the assay and to assess its reproducibility within/ between laboratories.

The radio synthesis and purification of [^{18}F]flortaucipir were optimized by using fully automatic procedures with less hazardous solvents and radiotracer doses which are applicable for clinical use (Shoup, Yokell et al. 2013, Gao, Wang et al. 2015, Holt, Ravert et al. 2016, Mossine, Brooks et al. 2017). The semi-quantitative standardized uptake value ratios (SUVr) of the most widely used time window of 80 to 100 minutes post injection correlated reasonably well with fully quantitative methods in cross-sectional studies (Baker, Lockhart et al. 2017, Barret, Alagille et al. 2017, Golla, Timmers et al. 2017, Hahn, Schain et al. 2017, Wooten, Guehl et al. 2017, Firouzian, Whittington et al. 2018, Heurling, Smith et al. 2019).

To test the reliability of [^{18}F]flortaucipir, test-retest (TRT) studies have been performed. In general, these studies show excellent TRT reproducibility (Devous, Joshi et al. 2018, Timmers, Ossenkoppele et al. 2019). For $SUVr_{80\text{-}100min}$ values of the percentage of change ranged between 1.5 to 3.3.% (Devous, Joshi et al. 2018) and 0.7 to 4.3% depending on the reference region and regions of interest. Quantitative methods (TRT ≈2%) performed slightly better than semi-quantitative measures such as SUVr (TRT ≈3%) (Timmers, Ossenkoppele et al. 2019). Recently, guidelines for visual interpretation of [^{18}F]flortaucipir images have been developed(Fleisher, Pontecorvo et al. 2020). This was based on visual [^{18}F]flortaucipir assessments performed by five readers that yielded high accuracy (~0.88) for assessing advanced tau stages (Braak V or VI) (Fleisher, Pontecorvo et al. 2020). More specific guidelines and training reader programs for nuclear medicine specialists have yet to be developed. This aim is considered partly achieved (Fig-1).

3.2.3. Phase 2. Secondary aim 2: To determine the relationship between biomarker measurements made on brain tissue and the biomarker measurements made on the non-invasive clinical specimen

Autopsy studies with ante-mortem [^{18}F]flortaucipir scans combined with post-mortem pathology showed strong associations between in vivo [^{18}F]flortaucipir uptake and the amount of post mortem tangles with rho's varying from 0.61 -0.93 (Smith, Puschmann et al. 2016, Fleisher, Pontecorvo et al. 2020, Lowe, Lundt et al. 2020). Importantly, these strong associations were found for AD like tau pathology and not for non-AD tau aggregates (Marquie, Normandin et al. 2017). Elevated *in vivo* [^{18}F]flortaucipir uptake was predominantly observed in Braak IV or higher (Fleisher, Pontecorvo et al. 2020, Lowe, Lundt et al. 2020). Braak V and higher was detected with a sensitivity ranging from 92.3% (95%CI, 79.7%-97.3%) to 100.0% (95%CI, 91.0%-100.0%) and specificity ranging from 52.0% (95% CI, 33.5%-70.0%) to 92.0% (95%CI, 75.0%-97.8%) (Fleisher, Pontecorvo et al. 2020). This aim is considered fully achieved (Fig-1).

3.2.4. Phase 2. Secondary aim 3: To assess factors (e.g. sex, age, etc.), associated with biomarker status or level in control subjects.

In cognitively normal elderly, [^{18}F]flortaucipir uptake is typically mostly confined to the medial temporal lobe (MTL) (Johnson, Schultz et al. 2016, Scholl, Lockhart et al. 2016, Pontecorvo, Devous et al. 2017, Tosun, Landau et al. 2017). The presence of amyloid-β may induce tau to spread outside of the MTL (Jacobs, Hedden et al. 2018, Ziontz, Bilgel et al. 2019), although neocortical tau was present in amyloid negative controls (Lowe, Bruinsma et al. 2018, Weigand, Bangen et al. 2020). Both cross-sectional (Johnson, Schultz et al. 2016, Sepulcre, Schultz et al. 2016, Wang, Benzinger et al. 2016, Lockhart, Scholl et al. 2017, Mishra, Gordon et al. 2017, Lowe, Wiste et al. 2018, Ramanan, Castillo et al. 2019, Sperling, Mormino et al. 2019, Ziontz, Bilgel et al. 2019, Pereira, Harrison et al. 2020) and antecedent amyloid accumulation (Tosun, Landau et al. 2017, Leal, Lockhart et al. 2018) was correlated with more (extra-)MTL [^{18}F]flortaucipir in the cognitively unimpaired. In addition, longitudinal [^{18}F]flortaucipir data also showed that an antecedent rise of amyloid-β was associated with a subsequent rise of tau accumulation in the inferior temporal lobe (Hanseeuw, Betensky et al. 2019). Recent studies found greater rates of tau accumulation (~+0.5% SUVr/year) in amyloid positive vs. negative control subjects (Jack, Wiste et al. 2018, Pontecorvo, Devous et al. 2019). However, another study observed accumulation of tau at similar rates for amyloid+ vs – cognitively normal individuals (Harrison, La Joie et al. 2019).

Two studies showed that APOE ε4carriers had increased levels of entorhinal [^{18}F]flortaucipir retention, however these effects were largely attributable to elevated amyloid-β levels (Ramanan, Castillo et al. 2019, Ghisays, Goradia et al. 2020), while studies in cognitively unimpaired controls using AD neuroimaging (ADNI) data showed that APOE ε4 was associated with increased [^{18}F]flortaucipir uptake in the MTL, independently of amyloid burden (Therriault, Benedet et al. 2019, Weigand, Thomas et al. 2020). Furthermore, a study in healthy controls (41.2% Aβ+) found higher tau SUVrs in the parahippocampal gyrus in ε3ε3 carriers compared to ε2ε3 carriers, after adjusting for amyloid. This potentially shows the protective effect of the ε2 allele, although this must be interpreted with caution since the number of ε2ε3 carriers was limited (n=11) (Pereira, Harrison et al. 2020).

The influence of sex on the amount of tau pathology in controls has yet to be determined, but mounting evidence is provided towards the conception that women harbor more tau pathology than men. One study in two independent cohorts of cognitively normal subjects found that in the presence of high amyloid burden, women had higher entorhinal tau load than man (Buckley, Mormino et al. 2019). This observation was confirmed in a study showing higher tau retention in temporo-parietal and frontal areas in women (Pereira, Harrison et al. 2020). Another study suggested that men have higher uptake mainly in the frontal and parietal white matter and thalamus than women (Ziontz, Bilgel et al. 2019), although this was hypothesized to be largely driven by non-specific binding.

Few studies have investigated the association between cardiovascular risk factors/small vessel disease and the amount of [^{18}F]flortaucipir retention. Higher cardiovascular risk score was related to higher tau uptake in temporal neocortical regions, in the presence of high amyloid-β burden (Rabin, Yang et al. 2019) When examining the separate components of the risk score, it was found that body mass index, treatment with antihypertensive medication, systolic blood pressure and smoking status all significantly contributed to this effect (Rabin, Yang et al. 2019). Another study including controls with a positive family history for sporadic AD, found no effect of vascular risk factors on entorhinal tau burden (Kobe, Gonneaud et al. 2020). A large study in 434 controls did not find an association between white mater hyperintensities on MRI and increased [^{18}F]flortaucipir retention (Graff-Radford, Arenaza-Urquijo et al. 2019).

Higher age is associated with higher [^{18}F]flortaucipir uptake in the temporal lobe (Sperling, Mormino et al. 2019, McSweeney, Pichet Binette et al. 2020), even independently of amyloid status (Lowe, Wiste et al. 2018, Maass, Lockhart et al. 2018). The observation of [^{18}F]flortaucipir uptake in the MTL in the absence of widespread neocortical amyloid plaques has been referred to as primary age-related tauopathy (PART)(Crary, Trojanowski et al. 2014). PART is a neuropathological description of the presence of NFTs in the MTL, basal forebrain and olfactory areas, without abundant amyloid-β pathology. Interestingly, both neuropathological studies (Braak and Braak 1997, Price and Morris 1999) and [^{18}F]flortaucipir PET studies (Jack, Wiste et al. 2018, Cho, Choi et al. 2019, Harrison, La Joie et al. 2019) indicate that NFTs may not consistently spread outside of these areas without amyloid-β.

Therefore, it could be argued that [^{18}F]flortaucipir PET uptake in the MTL in the absence of amyloid-β is an age related phenomenon and amyloid-β is necessary to trigger the spread of tau pathology.

African American ethnicity may be associated with higher [^{18}F]flortaucipir uptake. One smaller study demonstrated higher [^{18}F]flortaucipir SUVr's in the hippocampus and choroid plexus in the Black/ African American population when compared to white participants (Lee, Jacobs et al. 2018). These differences may be related to off-target binding to melanocytes in the choroid plexus causing spill-in into the hippocampus, since no differences were found in other regions of interest (ROIs). This is corroborated by another study which found that black race was associated with higher [^{18}F]flortaucipir retention in occipital, temporal and frontal clusters closely to meninges, which is known to contain high levels of neuromelanin (Ziontz, Bilgel et al. 2019).

A study in 325 individuals, mostly (90%) consisting of cognitively impaired controls found no effect of education on the amount of [^{18}F]flortaucipir retention (Ramanan, Castillo et al. 2019).

This aim is considered fully achieved (Fig-1).

3.2.5. Phase 2. Secondary aim 4: To assess factors associated with biomarker status or level in cognitively impaired subjects—in particular, disease characteristics such as stage, molecular features and prognosis.

There is a positive association between the level of cerebral amyloid load with greater [^{18}F]flortaucipir uptake in the brain (Johnson, Schultz et al. 2016, Wang, Benzinger et al. 2016, Maass, Landau et al. 2017, Pontecorvo, Devous et al. 2017, Whitwell, Graff-Radford et al. 2018, Dani, Wood et al. 2019, Ossenkoppele, Smith et al. 2019, Okafor, Nye et al. 2020). This is corroborated by longitudinal studies indicating that antecedent amyloid accumulation/status is predictive of higher rates of tau accumulation over time (Tosun, Landau et al. 2017, Jack, Wiste et al. 2018, Cho, Choi et al. 2019, Pontecorvo, Devous et al. 2019). Younger AD patients display higher levels of neocortical [^{18}F]flortaucipir uptake than older patients (Ossenkoppele, Schonhaut et al. 2016, Cho, Choi et al. 2017, Koychev, Gunn et al. 2017, Scholl, Ossenkoppele et al. 2017, Tosun, Landau et al. 2017, Lowe, Wiste et al. 2018, Whitwell, Graff-Radford et al. 2018), while older age is associated with greater [^{18}F]flortaucipir uptake specifically in the medial temporal lobe (Ossenkoppele, Schonhaut et al. 2016, Tosun, Landau et al. 2017, Whitwell, Graff-Radford et al. 2018).

Studies comprising cognitively normal and patients with MCI due to AD (Tosun, Landau et al. 2017) and MCI due to AD and AD dementia (Ossenkoppele, Lyoo et al. 2020) did not observe sex differences in [^{18}F]flortaucipir uptake.

Studies focusing on APOE genotype have reported conflicting results in how APOE genotype impacts the amount of [^{18}F]flortaucipir uptake in the brain. Two studies showed that amyloid+ APOE ε4 negative

carriers had higher [^{18}F]flortaucipir uptake in neocortical areas compared their APOE ε4 positive counterparts (Mattsson, Ossenkoppele et al. 2018, Whitwell, Graff-Radford et al. 2018). In a smaller study comprising various AD patients with non-amnestic presentations, APOE ε4 carriers showed greater temporal and parietal [^{18}F]flortaucipir uptake (Ossenkoppele, Schonhaut et al. 2016). Others found no association between APOE ε4 status and [^{18}F]flortaucipir uptake (Johnson, Schultz et al. 2016, Tosun, Landau et al. 2017). A larger study in 108 cognitively impaired patients found that APOE ε4 was associated with increased tau-PET uptake in the entorhinal cortex (Therriault, Benedet et al. 2019). In addition, women seem to be more susceptible to APOE ε4-associated accumulation of neurofibrillary tangles in MCI compared to males, although this effect was only observed in non-partial volume corrected data (Liu, Paranjpe et al. 2019).

To date, years of education was not associated with [^{18}F]flortaucipir uptake in some studies largely including MCI due to AD patients (Johnson, Schultz et al. 2016, Tosun, Landau et al. 2017). A study including 24 patients with AD dementia, showed that higher education was associated with higher [^{18}F]flortaucipir retention in more advanced Braak stages (Hoenig, Bischof et al. 2017). This aim is considered fully achieved (Fig-1).

3.3. Phase 3. Retrospective/ prospective/ longitudinal repository studies.

3.3.1. Phase 3. Primary aim 1: To evaluate, as a function of time in the prodromal stage (MCI), the capacity of the biomarker to predict conversion to AD dementia.

Few cross-sectional studies distinguished MCI-due to AD from non-AD (Ossenkoppele, Rabinovici et al. 2018, Jack, Wiste et al. 2019). AUCs ranging from 0.82 – 0.86 were found for distinguishing MCI due to AD from non-AD neurodegenerative diseases or controls. Since MCI due to AD is very likely to progress to AD, this provides preliminary evidence for the usefulness of [^{18}F]flortaucipir for predicting conversion to AD dementia.

Although not within the scope of this review (which is aimed at the prodromal phase of AD), note that a study in cognitively normal older adults showed that tau accumulation was associated with progression from preclinical AD to MCI (Hanseeuw, Betensky et al. 2019). Importantly, the amount of amyloid accumulation did not differ between the progressors (n=6) and stable (n=11) participants.

To date, there are no longitudinal studies available which predict the conversion of MCI patients to AD dementia. Since only cross-sectional data is available, this aim is considered preliminary achieved.

3.3.2. Phase 3. Primary aim 2: Define criteria for a positive diagnostic test for MCI due to AD, in preparation of Phase-4

Determining tau positivity requires careful selection of brain regions characterized by [^{18}F]flortaucipir uptake for defining an appropriate cut point. Various methods have been suggested, including approaches that recapitulate the neuropathological defined Braak stages (Scholl, Lockhart et al. 2016, Schwarz, Yu et al. 2016, Maass, Landau et al. 2017) as well as different regional and global qualitative measures (Wang, Benzinger et al. 2016, Jack, Wiste et al. 2017, Maass, Landau et al. 2017, Mishra, Gordon et al. 2017, Ossenkoppele, Rabinovici et al. 2018, Weigand, Bangen et al. 2020). The final selection may depend on the clinical question at stake (e.g. early detection, differential diagnosis, tracking disease progression over time). The jury is not yet out, but entorhinal cortex, inferior temporal cortex, a temporal meta-ROI (consisting of the entorhinal, amygdala, parahippocampal, fusiform, inferior temporal, and middle temporal ROI), temporoparietal cortex, whole-cortex and possibly data-driven ROIS are among the composite regions that are likely candidates for determination of tau PET positivity (Johnson, Schultz et al. 2016, Scholl, Lockhart et al. 2016, Jack, Wiste et al. 2017, Maass, Landau et al. 2017, Mishra, Gordon et al. 2017, Pontecorvo, Devous et al. 2017, Villemagne, Doré et al. 2017, Vogel, Mattsson et al. 2019). Some of these composite regions show a remarkable consistency across different studies, even though variability in image (pre)processing and acquisition exists, which bodies well for potential future clinical application of the tracer. A good example of this high consistency is the temporal meta-ROI, showing comparable SUVr cut offs across studies (1.2 -1.4) (Wang, Benzinger et al. 2016, Jack, Wiste et al. 2017, Maass, Landau et al. 2017, Mishra, Gordon et al. 2017, Ossenkoppele, Rabinovici et al. 2018, Lowe, Lundt et al. 2020). Regions involved earlier in AD, such as Braak stage I-II or the inferior temporal lobe, may be more sensitive to detect prodromal AD (Maass, Landau et al. 2017, Cho, Choi et al. 2019, Hanseeuw, Betensky et al. 2019). This is corroborated by longitudinal study which supports the temporal order of Braak staging with [^{18}F]flortaucipir PET, uptake rose sequentially from Braak I-II, through III-IV to V-VI (Baek, Cho et al. 2020). To date, there are no studies on visual assessment for solely MCI due to AD yet. However, two studies comprising of largely AD dementia patients, investigated the relationship between [^{18}F]flortaucipir retention with pathological tau burden and found that a minimum neuropathological Braak stage of IV was necessary to visually detect an elevated AD [^{18}F]flortaucipir PET signal (Fleisher, Pontecorvo et al. 2020, Lowe, Lundt et al. 2020). Furthermore an optimal threshold of 1.29 for the temporal meta-ROI was established to identify an diagnosis of on the AD spectrum with a sensitivity and specificity of 87% and 82%, respectively (Lowe, Lundt et al. 2020). This aim is considered partly achieved (Fig-1).

3.3.3. Phase 3. Secondary aim 1: To explore the impact of relevant covariates on the biomarker discrimination abilities before the clinical diagnosis.

To date, there are no studies which investigated the influence of certain factors on the diagnostic performance of [^{18}F]flortaucipir PET in MCI patients. However, regional tau differences are dependent

on age (Jack et al., 2017) and clinical stage (Cho et al., 2019), so we may have to use different cut-offs in different populations. Therefore, this aim was considered preliminary at the time of inclusion stop for this review (Fig-1).

3.3.4. Phase 3. Secondary aim 2: To compare biomarkers with a view to selecting those that are most promising.

Regional patterns of [^{18}F]Flortaucipir show close correspondence to hypometabolic patterns on [^{18}F]FDG PET (Ossenkoppele, Schonhaut et al. 2015, Bischof, Jessen et al. 2016, Ossenkoppele, Schonhaut et al. 2016, Dronse, Fliessbach et al. 2017). Similarly, several studies demonstrated strong anatomical overlap between tau pathology and brain atrophy (Cho, Choi et al. 2016, Wang, Benzinger et al. 2016, Xia, Makaretz et al. 2017, Das, Xie et al. 2018, Iaccarino, Tammewar et al. 2018, Mak, Bethlehem et al. 2018, Whitwell, Graff-Radford et al. 2018, Timmers, Ossenkoppele et al. 2019, Josephs, Tosakulwong et al. 2020, La Joie, Visani et al. 2020, Okafor, Nye et al. 2020) in MCI and AD patients. In prodromal AD, tau PET was slightly stronger associated with lower scores on cognitive tests than amyloid PET and cortical thickness, suggesting that tau PET is more sensitive than amyloid PET /cortical thickness in measuring cognitive changes early in the disease (Ossenkoppele, Smith et al. 2019). Two studies compared tau PET with MRI atrophy measures in order to predict the diagnosis of AD (Ossenkoppele, Smith et al. 2019). For both the diagnosis of MCI/ AD dementia vs. cognitively unimpaired subjects (Mattsson, Insel et al. 2019) and vs. non-AD neurodegenerative disorders (Ossenkoppele, Rabinovici et al. 2018), [^{18}F]Flortaucipir (AUCs >0.9) outperformed established MRI measurements such as hippocampal volumes (AUC of ~0.6), AD signature cortical thickness (AUCs of ~0.8) or whole-brain cortical thickness (AUC of ~0.5). To date, no studies have compared the predictive value of these different imaging modalities for the conversion from MCI to AD dementia.

Several cross-sectional studies compared CSF tau biomarkers with [^{18}F]flortaucipir tau PET (Gordon, Friedrichsen et al. 2016, Mattsson, Scholl et al. 2017, La Joie, Bejanin et al. 2018, Mattsson, Smith et al. 2018, Janelidze, Stomrud et al. 2020, Meyer, Binette et al. 2020, Okafor, Nye et al. 2020, Wolters, Ossenkoppele et al. 2020). Two studies compared the diagnostic accuracy for phosphorylated tau (p-tau), total tau (t-tau) and [^{18}F]flortaucipir in distinguishing MCI /AD dementia versus cognitively unimpaired (Mattsson, Smith et al. 2018) or non-AD neurodegenerative disease (La Joie, Bejanin et al. 2018). A [^{18}F]flortaucipir temporal meta-ROI was better in distinguishing AD dementia from controls (AUC 1.0 vs. t-tau, AUC 0.88; p-tau, AUC 0.89), but all tau biomarkers performed equally well in distinguishing MCI from cognitively normal ([^{18}F]flortaucipir, AUC 0.92; t-tau, AUC 0.86; p-tau, AUC 0.94) (Mattsson, Smith et al. 2018). Comparable excellent classification was also seen for [^{18}F]flortaucipir and CSF p-tau for the differential diagnosis AD vs. non-AD dementias (AUCs 0.92-0.94) (La Joie, Bejanin et al. 2018). It is important to note that CSF tau biomarkers and [^{18}F]flortaucipir PET

probably reflect different aspects of tau pathology, which become apparent in the temporal difference of "becoming abnormal" between the biomarkers. That is, CSF p-tau probably changes early in the disease course, and plateaus in early AD (Mattsson, Scholl et al. 2017, Mattsson-Carlgren, Andersson et al. 2020, Meyer, Binette et al. 2020, Wolters, Ossenkoppele et al. 2020), while [^{18}F]flortaucipir PET likely becomes abnormal after CSF tau biomarkers (Mattsson-Carlgren, Andersson et al. 2020) and continues to increase over time with advancing disease stage (Jack, Wiste et al. 2018, Cho, Choi et al. 2019, Hanseeuw, Betensky et al. 2019, Harrison, La Joie et al. 2019, Pontecorvo, Devous et al. 2019, Baek, Cho et al. 2020).

Emerging evidence demonstrated that binary classifications as well as continuous levels of plasma tau phosphorylated at threonine 181 (p-tau$_{181}$) are strongly associated with [^{18}F]flortaucipir retention (Janelidze, Mattsson et al. 2020, Thijssen, La Joie et al. 2020). Furthermore, plasma p-tau$_{181}$ accurately discriminated AD dementia from a variety non-AD neurodegenerative disorders (for example from FTLD or a variety of non-AD disorders with AUCs of 0.89 and 0.93, respectively) (Janelidze, Mattsson et al. 2020, Thijssen, La Joie et al. 2020), although slightly worse than [^{18}F]flortaucipir PET (AUC of 0.98) (Janelidze, Mattsson et al. 2020).

Currently, there are no studies available that compare the ability of these biomarkers to identify those MCI subsequently progressing to AD dementia. Therefore, this aim was preliminary achieved (Fig-1).

3.3.5. Phase 3. Secondary aim 3: To develop algorithms for the biomarker-based diagnosis of MCI in preparation of Phase-4.

There is no study proposing an algorithm combining [^{18}F]flortaucipir to other biomarkers to predict cognitive decline in MCI. A longitudinal study among older persons without dementia at baseline found that a model combining input from amyloid PET, [^{18}F]flortaucipir PET and MRI cortical thickness data provided the most optimal prediction of memory decline (Jack, Wiste et al. 2019). The evidence for this aim is considered preliminary (Fig-1).

3.3.6. Phase 3. Secondary aim 4: To determine an interval able to detect a meaningful change of biomarker status or level in progressing MCI

Few studies (Jack, Wiste et al. 2018, Cho, Choi et al. 2019, Hanseeuw, Betensky et al. 2019, Harrison, La Joie et al. 2019, Pontecorvo, Devous et al. 2019, Baek, Cho et al. 2020) have investigated [^{18}F]flortaucipir uptake longitudinally with a maximum time interval of 2 years. Results were mixed and potentially affected by methodological decisions regarding the choice of reference region, regions of interest and partial volume correction methods. In MCI patients, the patterns of MCI patients progressing to AD differed from the stable MCI subjects during a follow-up period of two years (Cho, Choi et al. 2019).

Progressors showed an increase in all cortical regions, except for the sensorimotor cortex, while the cognitively stable participants showed increases in the inferior temporal cortex. Another longitudinal study (with partially overlapping participants from (Cho, Choi et al. 2019)) showed that the annual change in tau accumulation within all Braak regions, was intermediate in MCI patients relative to cognitively unimpaired and dementia patients (Baek, Cho et al. 2020). There is no notion of clinical progression of the MCI patients included in this study.

Other studies did not show results of MCI patients separately from participants with AD dementia (Jack, Wiste et al. 2018, Harrison, La Joie et al. 2019), but differences were observed in rate of accumulation in amyloid positive cognitively impaired (+3%-5% SUVr/ year) vs. unimpaired (+0.5-3% SUVR/year) subjects in a meta-ROI comprising AD-specific areas of the temporal cortex (Jack, Wiste et al. 2018, Harrison, La Joie et al. 2019). Consistently with the requirement that the proper achievement of the downstream validation steps depends on the full achievement of the above mentioned steps, the validation of [^{18}F]flortaucipir did not yet enter the validation Phases-4-5. This aim was preliminary achieved (Fig-1).

4. Discussion

With this work we assessed the maturity of [^{18}F]flortaucipir as a biomarker of brain tauopathy according to the 5-phase framework, which was originally developed for oncology biomarkers (Pepe, Etzioni et al. 2001). We adapted this framework to study populations including MCI-due-to-AD and AD dementia (Boccardi, Gallo et al. 2017), and used it to critically evaluate for which validation steps sufficient evidence has been provided in the literature and to identify the validation steps that require additional research.

We considered phase 1 fully achieved based on (pre)clinical studies that demonstrated the rationale for using [^{18}F]flortaucipir. [^{18}F]flortaucipir binds with high affinity to AD PHFs of tau (Chien, Bahri et al. 2013, Xia, Arteaga et al. 2013, Marquie, Normandin et al. 2015, Lowe, Curran et al. 2016) and the *in vivo* kinetics of [^{18}F]flortaucipir are favorable (Baker, Lockhart et al. 2017, Barret, Alagille et al. 2017, Golla, Timmers et al. 2017, Hahn, Schain et al. 2017, Wooten, Guehl et al. 2017). The primary aim of phase 2 was also considered fully achieved. A large multi-center study found an excellent diagnostic accuracy (AUC = 0.97) of [^{18}F]flortaucipir to distinguish patients with AD dementia from controls (Ossenkoppele, Rabinovici et al. 2018). Moreover, the test-retest reliability of [^{18}F]flortaucipir was excellent, with percentages of change ranging from ~1 - 4% (Devous, Joshi et al. 2018, Timmers, Ossenkoppele et al. 2019). For the secondary aims of phase 2, ante-mortem [^{18}F]flortaucipir was strongly associated with post-mortem tau burden (Fleisher, Pontecorvo et al. 2020, Lowe, Lundt et al. 2020). Multiple studies

investigated the effect of confounders, such as age, sex, APOE, education and vascular risk factors on the amount of [^{18}F]flortaucipir in both controls and AD patients. Therefore, the majority of the secondary aims of phase 2 are fully achieved. Phase 3 first primary aim was preliminarily achieved and the secondary primary aim was partly achieved. Only few longitudinal studies in MCI patients are available and defining tau PET-positivity is challenging because many factors (e.g. ROI definition, demographic variables and disease severity) can impact the threshold. Nevertheless, encouraging results were obtained as studies in multiple independent cohorts have shown that, despite the substantial variation in image (pre)processing and acquisition, quantitative cut-offs for a temporal composite ROI were largely comparable (Wang, Benzinger et al. 2016, Jack, Wiste et al. 2017, Maass, Landau et al. 2017, Mishra, Gordon et al. 2017, Ossenkoppele, Rabinovici et al. 2018). The secondary aims of phase 3 (i.e. comparison between or combining different biomarkers) were preliminarily achieved, because ability of these biomarkers to accurately detect those MCI progressing to AD at follow-up was not determined. Although the accumulation of tau is probably clinically meaningful (Jack, Wiste et al. 2018, Cho, Choi et al. 2019, Hanseeuw, Betensky et al. 2019, Pontecorvo, Devous et al. 2019), only preliminary evidence is available to determine the optimal interval for repeating [^{18}F]flortaucipir PET scans over time. The aims of phase 4 and 5 (i.e. prospective diagnostic studies and disease-control studies) were not achieved. This kind of work is necessary to coordinate efforts across independent research groups. Greater awareness of completed steps, research gaps and priorities based on a sound consensual methodological framework guarantees the cost-effectiveness and boosting of the validation procedure.

Our analysis identified at least four areas of research that require further investigation to reach full maturity for [^{18}F]flortaucipir PET as a biomarker for brain tauopathy. First, procedures and criteria for [^{18}F]flortaucipir PET positivity need to be refined and compared against other (established) biomarkers of AD. The proposed visual read metric for [^{18}F]flortaucipir PET (Fleisher, Pontecorvo et al. 2020) has shown to benefit from a complementary quantitative cut-off that reduces the number of false positive cases. It is possible that different thresholds are required, as there is substantial regional variability the accumulation of tau. For example, visual assessment of early to intermediate tau-specific regions such as Braak stage I-II or the inferior temporal lobe may be challenging, as previous studies showed that a positive visual read was associated with tau pathology in Braak stage IV or higher (Fleisher, Pontecorvo et al. 2020, Lowe, Lundt et al. 2020). Furthermore, not all AD patients adhere to the stereotypical spread of tau pathology as proposed by neuropathological studies (Braak and Braak 1991), as a substantial proportion of AD present with a neocortical-predominant and hippocampal-sparing type of AD (Ossenkoppele, Lyoo et al. 2020, Sintini, Graff-Radford et al. 2020). For the comparison with other tau biomarkers, mounting evidence so far points into the direction that CSF p-tau may be more sensitive in detecting tau pathology in the earliest clinical phases of AD (Mattsson, Scholl et al. 2017, Mattsson-Carlgren, Andersson et al. 2020, Meyer, Binette et al. 2020, Wolters, Ossenkoppele et al. 2020), although diagnostic accuracy to discriminate MCI patients showed comparable results (Mattsson, Smith et al.

2018). At the dementia stage, contrary to CSF p-tau, [^{18}F]flortaucipir PET has not yet reached a plateau in the neocortex (Jack, Wiste et al. 2018, Cho, Choi et al. 2019, Hanseeuw, Betensky et al. 2019, Harrison, La Joie et al. 2019, Pontecorvo, Devous et al. 2019, Baek, Cho et al. 2020), and can therefore more accurately track disease progression. In addition, compared to tau biofluid biomarkers, [^{18}F]flortaucipir PET has the advantage to regionally assess the extent of tau pathology.

A second gap to be filled as research priority is to assess the influence of covariates on determination of [^{18}F]flortaucipir positivity. Many studies identified modifiers of tau accumulation in controls, including higher age (Scholl, Ossenkoppele et al. 2017, Lowe, Wiste et al. 2018, Maass, Lockhart et al. 2018, Sperling, Mormino et al. 2019, McSweeney, Pichet Binette et al. 2020), baseline and longitudinal change in amyloid burden (Johnson, Schultz et al. 2016, Sepulcre, Schultz et al. 2016, Wang, Benzinger et al. 2016, Lockhart, Scholl et al. 2017, Mishra, Gordon et al. 2017, Tosun, Landau et al. 2017, Jack, Wiste et al. 2018, Leal, Lockhart et al. 2018, Lowe, Wiste et al. 2018, Hanseeuw, Betensky et al. 2019, Pontecorvo, Devous et al. 2019, Ramanan, Castillo et al. 2019, Sperling, Mormino et al. 2019, Ziontz, Bilgel et al. 2019, Pereira, Harrison et al. 2020), female sex (Buckley, Mormino et al. 2019, Pereira, Harrison et al. 2020) and APOE ε4 status (Therriault, Benedet et al. 2019). In AD patients, lower age was associated with a higher neocortical tau burden (Ossenkoppele, Schonhaut et al. 2016, Cho, Choi et al. 2017, Koychev, Gunn et al. 2017, Scholl, Ossenkoppele et al. 2017, Tosun, Landau et al. 2017, Lowe, Wiste et al. 2018, Whitwell, Graff-Radford et al. 2018), whereas higher age was associated with higher [^{18}F]flortaucipir in the medial temporal lobe (Ossenkoppele, Schonhaut et al. 2016, Tosun, Landau et al. 2017, Whitwell, Graff-Radford et al. 2018). Future studies are needed to assess whether flexible [^{18}F]flortaucipir positivity thresholds or target regions of interest should be implemented based on patient-specific demographic, clinical or genetic information.

Finally, there is a clear need for studies that prospectively assess whether [^{18}F]flortaucipir PET impacts patients management, healthcare outcomes and costs, as well as its feasibility in a clinical setting.

This work has some limitations. First, although adhering to sound methodology, the fulfillment of each Aim should be based on a more thorough evidence assessment examining many possible sources of bias (e.g., Gutyatt et al 2011 (Guyatt, Oxman et al. 2011) “GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables”). Our online tables (https://drive.switch.ch/index.php/s/4reUTSuqNZHyIC8) are meant to help this development as a next step forward in a systematic assessment of the validation of AD biomarkers. Second, for the fulfillment of Phase 1 and 2 the gold standard of neuropathology is required. AD tissue in combination with ante-mortem imaging data is much less accessible than for example in oncology, the disease for which the original Geneva Roadmap was developed (Pepe, Etzioni et al. 2001). It is important to note that we also considered feasibility issues when assessing the maturity of the different aims. Third,

[^{18}F]flortaucipir is situated in a dynamic field of research characterized by rapid development and progression. When interpreting the analysis presented here, one should note that our inclusion stop for published studies was May 5th 2020 and that more validation steps within framework might have been (more) complete(d) in the near future.

Conclusion

This review systematically investigated[^{18}F]flortaucipir PET studies in order to assess the validation maturity of [^{18}F]flortaucipir PET and define its clinical validity for the diagnosis of AD. Current literature provides partial evidence for clinical utility of [^{18}F]flortaucipir PET. The aims for phase 1 and 2 were largely achieved. In vivo [^{18}F]flortaucipir PET shows excellent diagnostic accuracy for AD and promising results for the validation with autopsy studies. Phase 3 studies are currently ongoing. Further studies in phase 4 and 5 including representative MCI populations and focusing on health care outcomes are required to establish full maturity.

Compliance with Ethical standards

Conflict of interest

Wolters, Dodich, Boccardi, Corre, Drzezga, Nordberg, Frisoni and Ossenkoppele report no disclosures.

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No other potential conflicts of interest relevant to this article exist.

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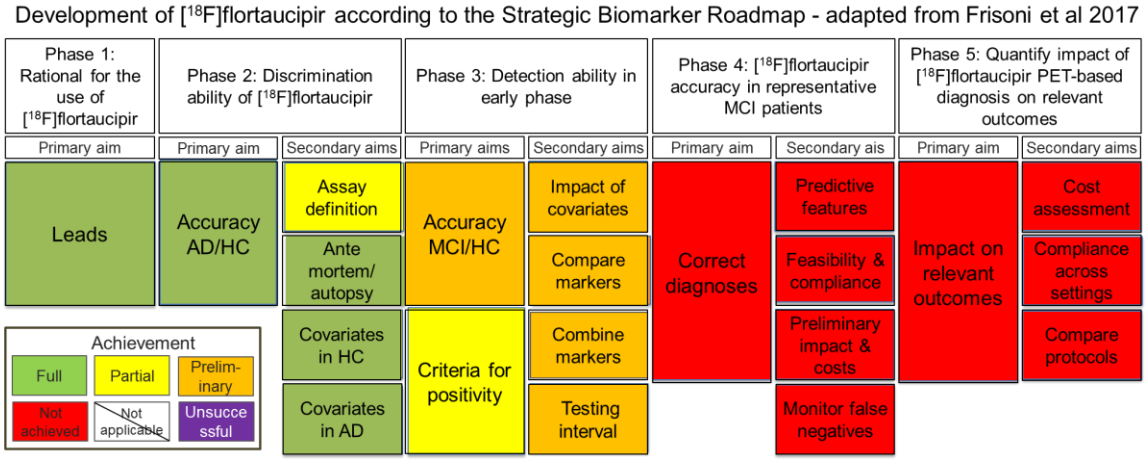
Figure 1 The development of [18F]flortaucipir according to the Strategic Biomarker Roadmap



Supplementary data

Supplementary table 1. Strings used as reference for the harmonized literature searches of the [^{18}F]flortaucipir review on the maturity of biomarkers of mild cognitive impairment due to Alzheimer's disease.

		Aim-specific key words string
Phase 1: preclinical exploratory studies	**Primary aim:** To identify leads for potentially useful biomarkers and prioritize identified leads.	(e)
Phase 2: clinical assay development for clinical disease	**Primary aim:** To estimate TPR and FPR or ROC curve for the assay and to assess its ability to distinguish subjects with and without disease.	("accuracy" OR "sensitivity" OR "Specificity" OR "ROC" OR "predictive value") AND (a) AND (b) AND (e)
	Secondary aim 1: To optimize procedures for performing the assay and to assess the reproducibility of the assay within and between laboratories.	("standardization" OR "visual" OR "measure" OR "assessment" OR "reading" OR "quantification") AND ("reproducibility OR "reliability" OR "agreement") AND ("Alzheimer") AND (a) AND (e)
	Secondary aim 2: To determine the relationship between biomarker tissue measurements made on tissue (phase 1) and the biomarker measurements made on the noninvasive clinical specimen (phase 2).	("autopsy" OR "autoptic" OR "pathology" OR "neuropatholog*" OR "histopathol*") AND (a) AND (e)
	Secondary aim 3: To assess factors (e.g. sex, age, etc.), associated with biomarker status or level in control subjects. If such factors affect the biomarker, thresholds for test positivity may need to be defined separately for target subpopulations.	("effect" OR "association" OR "covariates") AND ("factor" OR "habit" OR "age" OR "sex" OR "gender" OR "education" OR "life-style" OR "risk factor") AND (b) AND (e)
	Secondary aim 4: To assess factors associated with biomarker status or level in diseased subjects—in particular, disease characteristics.	("effect" OR "association" OR "covariates") AND ("factor" OR "habit*" OR "age" OR "sex" OR "gender" OR "education" OR "life-style" OR "risk factor*") AND (a) OR (c) AND (e)
Phase 3: Prospective repository studies	**Primary aim 1:** To evaluate the capacity of biomarkers to detect pre-clinical disease and define criteria for a positive biomarker test in preparation for phase 4.	("follow-up" OR "followup" OR "conversion" OR "progression" OR "decline" OR "predict") AND (c) AND (e)
	Primary aim 2::	("cut-off" OR "cut-point" OR "measure" OR "assessment") and (e)
	Secondary aim 1: To explore the impact of covariates on the discriminatory abilities of the biomarker before clinical diagnosis.	("effect" OR "association" OR "covariates") AND ("factor" OR "habit" OR "age" OR "sex" OR "gender" OR "education" OR "life-style" OR "risk factor") AND ((a) OR (b) OR (c)) AND (e)

	Secondary aim 2: To compare markers with a view to selecting those that are most promising.	("follow-up" OR "followup" OR "conversion" OR "progression" OR "decline" OR "predict" OR "cut-off" OR "cut-point" OR "measure" OR "assessment") AND ("combinat*" OR "associat*" OR "compar*") AND (a) AND (c) AND (e)
	Secondary aim 3: To develop algorithms for positivity based on combinations of markers.	("follow-up" OR "followup" OR "conversion" OR "progression" OR "decline" OR "predict" OR "cut-off" OR "cut-point" OR "measure" OR "assessment") AND ("combinat*" OR "associat*" OR "compar*") AND (a) AND (c) AND (e)
	Secondary aim 4: To determine a biomarker testing interval for phase 4 if repeated testing is of interest.	("follow-up" OR "followup" OR "conversion" OR "progression" OR "decline" OR "predict" OR "cut-off" OR "cut-point" OR "measure" OR "assessment") AND ("combinat" OR "associat" OR "compar") AND (a) AND (c) AND (e)
Phase 4: Prospective Diagnostic Studies	**Primary aim:** To determine the operating characteristics of the biomarker-based test in a relevant population by determining the detection rate and the false referral rate. Studies at this stage involve testing people and lead to diagnosis and treatment.	("diagnosis" OR "treatment") AND (a) AND (c) AND (e)
	Secondary aim 1: To describe the characteristics of disease detected by the biomarker test—in particular, with regard to the potential benefit incurred by early detection.	("clinical diagnosis" OR "treatment" OR "memory clinic") AND ("benefits"OR "outcome" OR "improve") AND (a) AND (c) AND (e)
	Secondary aim 2: To assess the practical feasibility of implementing the case finding program and compliance of test-positive subjects with work-up and treatment recommendations.	("clinical diagnosis" OR "treatment" OR "memory clinic") AND ("benefit" OR "compliance" OR "mortality" OR"morbidity" OR "QoL" OR "quality of life") AND (a) AND (e)
	Secondary aim 3: To make preliminary assessments of the effects of biomarker testing on costs and mortality associated with the disease.	("clinical diagnosis" OR "treatment" OR "memory clinic") AND ("benefit" OR "compliance" OR "mortality" OR" morbidity" OR "QoL" OR "quality of life"AND (a) AND (e)
	Secondary aim 4: To monitor disease occurring clinically but not detected by the biomarker testing protocol.	("clinical diagnosis" OR "memory clinic" OR "criteria" OR "recommendation") AND ("accuracy" OR "sensitivity" OR"specificity" OR"ROC" OR "predictive value" OR "concordance" OR "confirm" OR "negative detection rate" OR "negative referral rate" OR "false negative rate") AND (a) AND (e)
Phase 5: Disease Control Studies	**Primary aim:** To estimate the reductions in disease-associated mortality, morbidity, and disability afforded by biomarker testing.	("diagnosis" OR "detection") AND ("benefit" OR "compliance" OR "mortality" OR "morbidity" OR "QoL" OR "quality of life" OR "financial impact" OR "cost" OR "effectiveness") AND (a) AND (e)
	Secondary aim 1: To obtain information about the costs of biomarker testing and treatment and the cost per life saved or per quality-adjusted life year	("diagnosis" OR "detection") AND ("benefit" OR "compliance" OR "mortality" OR "morbidity" OR "QoL" OR "quality of life" OR "financial impact" OR "cost" OR "effectiveness")AND (a) AND (c) AND (e)
	Secondary aim 2: To evaluate compliance with testing and work-up in a diverse range of settings.	("diagnosis" OR "detection") AND ("benefit" OR "compliance" OR "mortality" OR "morbidity" OR "QoL" OR "quality of life" OR "financial impact" OR "cost" OR "effectiveness") AND (a) AND (e)

	Secondary aim 3: To compare different biomarker testing protocols and/or to compare different approaches to treating test positive subjects in regard to effects on mortality and costs.	("diagnosis" OR "treatment") AND ("protocol" OR "recommendation" OR "criteria") AND ("benefit" OR "compliance" OR "mortality" OR "morbidity" OR "QoL" OR "quality of life") AND ("financial impact" OR "cost" OR "effectiveness") AND (a) AND (e)

(a) ("Alzheimer*")
(b) ("Healthy Controls" OR "Cognitively normal" OR "controls" OR "normal").
(c) ("MCI" OR "mild cognitive impairment" OR"prodromal")
(d) (other disease/e.g. DLB – if pertinent)
(e) ("T807" OR "AV1451" OR "AV-1451" OR "flortaucipir")

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