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Featured Article

AMYPAD Diagnostic and Patient Management Study: Rationale and design

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Abstract

Introduction: Reimbursement of amyloid–positron emission tomography (PET) is lagging due to the lack of definitive evidence on its clinical utility and cost-effectiveness. The Amyloid Imaging to Prevent Alzheimer's Disease–Diagnostic and Patient Management Study (AMYPAD-DPMS) is designed to fill this gap.

Methods: AMYPAD-DPMS is a phase 4, multicenter, prospective, randomized controlled study. Nine hundred patients with subjective cognitive decline plus, mild cognitive impairment, and dementia possibly due to Alzheimer's disease will be randomized to ARM1, amyloid-PET performed early in the diagnostic workup; ARM2, amyloid-PET performed after 8 months; and ARM3, amyloid-PET performed whenever the physician chooses to do so.

Endpoints: The primary endpoint is the difference between ARM1 and ARM2 in the proportion of patients receiving a very-high-confidence etiologic diagnosis after 3 months. Secondary endpoints address diagnosis and diagnostic confidence, diagnostic/therapeutic management, health economics and patient-related outcomes, and methods for image quantitation.

Expected Impacts: AMYPAD-DPMS will supply physicians and health care payers with real-world data to plan management decisions.

Keywords: Amyloid-PET; Alzheimer's disease; Mild cognitive impairment; Subjective cognitive decline; Clinical validity; Cost-effectiveness

1. Background

Amyloid–positron emission tomography (PET) can reliably detect senile plaques made of amyloid-β [1–3], hallmarks of Alzheimer's disease (AD), and fluorinated ligands are approved in several countries [4–9]. Nevertheless, reimbursement is lagging due to the lack of definitive evidence supporting its clinical utility and cost-effectiveness in the diagnostic workup.

An observational study in the USA, the Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) study [10], aims to assess the clinical utility of amyloid-PET on more than 18,000 patients aged 65+ years meeting the appropriate use criteria for amyloid-PET prescription published by the Amyloid Imaging Taskforce (AIT) [11,12]. This study is currently assessing the impact of amyloid-PET on patient management (change of at least one of the following endpoints: AD drug therapy, other drug therapy, and counseling about safety and future planning) and on the use of health care resources (hospital admissions and emergency room visits) in amyloid-PET-known compared to matched patients not undergoing amyloid-PET over 12 months. Preliminary results on the first 3979 patients showed a considerable change in patient management in 68% of mild cognitive impairment (MCI) and in 66% of dementia patients following amyloid-PET [13]. These results are in good agreement with a recent review on the clinical utility of amyloid imaging, reporting a change in patient management in 64% of patients, as well as a change in diagnosis in 29%, and in medications in 38% of patients [14].

Amyloid Imaging to Prevent Alzheimer's Disease (AMYPAD) is a collaborative research initiative aimed to improve diagnosis and management and to accelerate the development of disease-modifying treatments through the utilization of amyloid-PET [15]. This 5-year program is part of the Innovative Medicines Initiative, a joint undertaking between the European Commission and the European Federation of Pharmaceutical Industries and Associations. A total of 6000 scans will be performed in the whole AMYPAD project split 50:50 between the PET imaging agents [^{18}F]florbetaben (trade name NeuraCeq, Piramal Imaging) and [^{18}F]flutemetamol (trade name Vizamyl, GE Healthcare). AMYPAD will have two main clinical studies. In the prognostic and natural history study (AMYPAD-PNHS), amyloid-PET will be carried out in the context of its sister project EPAD (European Prevention of Alzheimer's Dementia) aiming to set up a cohort of nondemented persons at high risk of AD who will be enrolled in preventive pharmacologic trials [16]. The second component is the Diagnostic and Patient Management Study (AMYPAD-DPMS), which aims to investigate the clinical utility of amyloid-PET in a controlled but realistic clinical setting of patients with subjective cognitive decline (SCD) plus (SCD+) [17], MCI, and dementia possibly due to AD. This article aims to describe the rationale, design, methods, and expected results and impact of AMYPAD-DPMS.

2. Rationale

The clinical-scientific space of AMYPAD-DPMS is that of the introduction of amyloid-PET in the routine clinical practice in the diagnostic workup of patients with suspect AD. Despite overwhelming evidence on the analytical [1–3] and clinical validity of amyloid-PET [18], evidence on the clinical utility is still limited (Table S1 in Supplementary Material). Indeed, most of the studies published so far [19–28] are only observational and lack proper study designs (e.g., parallel control groups) for a systematic and definitive assessment of the amyloid-PET clinical utility. Moreover, and most importantly, evidence on real-life effectiveness

and cost-effectiveness in the absence of disease-modifying therapies is lacking [29]. The IDEAS study will provide strong evidence, but its results are not directly transferable to the European health care setting, which is quite different from that of the USA.

As a consequence of the limited available evidence, payers (e.g., public health care systems or private health care insurances) are either not reimbursing the amyloid-PET examination or restricting reimbursement to extremely narrow indications (e.g., very specific categories of patients) or at the rate of the much cheaper FDG-PET (covering only part of the costs, e.g., the PET scan itself, and leaving the remaining costs, e.g., the amyloid tracer purchase, to be paid by the patient) [30]. AMYPAD-DPMS aims to fill this evidence gap by testing the hypothesis that patients undergoing amyloid-PET early on in their diagnostic workup receive a very-high-confidence etiologic diagnosis earlier than patients undergoing amyloid-PET later or never, and by providing relevant information about health economics variables (savings on other diagnostic examinations, unnecessary drug treatment, hospitalizations and other medical consultations, etc.). We also hypothesize that earlier and more confident diagnosis is followed by more frequent inclusion in AD clinical trials, earlier and more frequent adoption of pharmacologic and nonpharmacologic symptomatic treatments, lower use of medical resources, and better patient quality of life (lower anxiety, better coping). The diagnostic questions we wish to address are those related to the traditional differential diagnosis of AD in patients with dementia, early and differential diagnosis of AD in patients with MCI, and to the more contentious issue of dementia risk profiling in SCD. In AMYPAD-DPMS, patients with SCD satisfy the Subjective Cognitive Decline Initiative (SCD-I) Working Group criteria for SCD+ (self-reported cognitive complaint, plus features increasing the likelihood of preclinical AD) [17]. Patients with SCD+ have a higher rate of conversion to MCI than patients with SCD not meeting the criteria for SCD+ (18.9% vs. 5.6% [31]). The study design rests on some assumptions.

1. *Generalizability of results.* Although the design of any clinical trial inevitably diverges from clinical practice, we assume that the results of a study designed by leveraging on the typical memory clinic practice would be applicable to the practices of general memory clinics.
2. *Diagnostic workup.* We assume that memory clinics worldwide share a typical workup featuring the following components: a first consultation by the medical specialist collecting history, carrying out screening cognitive tests, neurological physical and psychiatric assessment, and prescription of complementary examinations; based on information collected during the first consultation, a syndromic diagnosis (SCD, MCI, dementia) can be made; a structural scan (CT or MRI) done in virtually 100% of cases and preliminary to further biomarker assessment; the prescription or collection of biomarkers (e.g., cerebrospinal fluid and/or FDG-PET) takes place after the structural scan in a variable number of cases; the diagnostic workup strives to achieve an etiologic diagnosis on top of the syndromic diagnosis; once the specialist is confident enough, the etiologic diagnosis is communicated to the patient, and prescription of pharmacologic and non-pharmacologic treatments takes place at the end of the diagnostic workup, in general within 3 months and at the latest within 6 months from the first visit.
3. *Diagnostic reasoning framework.* We assume that specialists share the abstract notion of what constitutes a high/low likelihood that symptoms are due to AD; and that the higher the likelihood, the higher the confidence in an etiologic diagnosis of AD, the lower the likelihood, the higher the confidence in an etiologic diagnosis of non-AD (Fig. 1). We also assume that confidence in an etiologic diagnosis of AD/non-AD can be loosely operationalized into a percentage of confidence; and specialists aim to achieve the highest possible confidence, ideally $\geq$90%.
4. *Diagnostic criteria.* We assume that most memory clinics refer to the 2011 National Institute on Aging and Alzheimer's Association criteria [32–34] for the AD diagnosis, either implicitly or explicitly. The recent revision of the National Institute on Aging and Alzheimer's Association criteria [35], with its agnostic descriptive approach, will likely change research and clinical approaches to AD. When this happens, the AMYPAD-DPMS results may need to be reinterpreted.

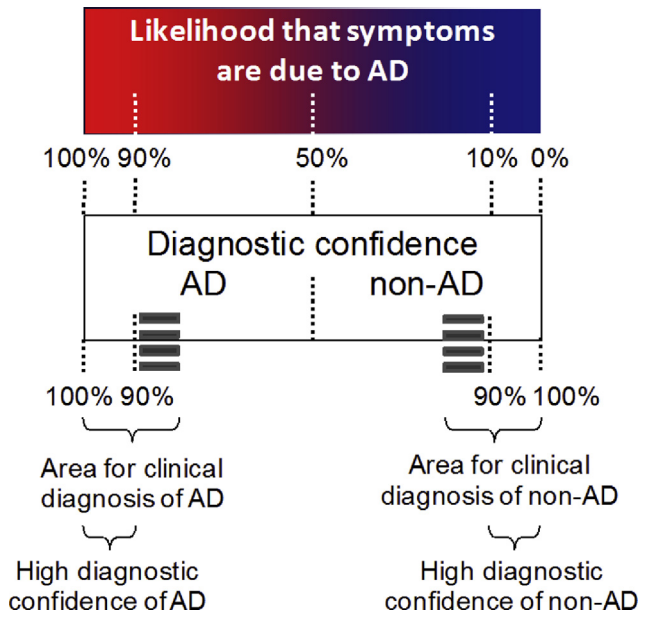

Fig. 1. Diagnostic reasoning framework in AMYPAD-DPMS. Abbreviations: AD, Alzheimer's disease; AMYPAD-DPMS, Amyloid Imaging to Prevent Alzheimer's Disease–Diagnostic and Patient Management Study.

5. *Consequences of an etiologic diagnosis.* We assume that an accurate etiologic diagnosis can potentially impact management in patients with dementia (especially regarding acetylcholinesterase inhibitor (AChEI) treatment); while there is lesser agreement on the pharmacologic management of patients with MCI, a number of specialists prescribe AChEIs off-label; and an etiologic diagnosis is not possible in SCD+; however, in this population, amyloid-PET could be used for risk profiling [36]. Moreover, while a positive scan can confirm a previous AD diagnosis or increase the likelihood of AD, a negative scan excludes AD from the differential diagnosis potentially leading to discharge in patients with SCD, and to other diagnostic examinations or a milder prognosis in those with MCI or dementia [37].
6. *Frequency of amyloid pathology.* The prevalence of amyloid pathology increases from age 50 to 90 years from 12% to 43% in SCD (may be higher in SCD+), and from 27% to 71% in MCI [38], whereas decreases from age 50 to 90 years from 93% to 79% in patients with AD dementia [39].

3. Methods

3.1. Participants

Nine hundred persons 50 to 85 years of age will be enrolled: 300 SCD+, 300 MCI, and 300 with dementia where AD is in the differential diagnosis. All consecutive patients coming to observation to a participating memory clinic with a request for diagnosis and fulfilling inclusion and exclusion criteria will be eligible for enrollment. Inclusion and exclusion criteria (Tables 1 and 2) were drafted to include all patients with cognitive complaints eligible to undergo a diagnostic workup, with the possibility that complaints are due to AD, and where an accurate etiologic diagnosis may have some impact on patient management and quality of life.

3.2. Setting

The 8 EPAD memory clinics will enroll patients to AMYPAD-DPMS (Fig. 2). We expect each center contributing 112 participants. We acknowledge that some features of participating academic memory clinics might limit the generalizability of the results of the study to the nonacademic memory clinics consulting the large majority of patients from the general population. Indeed, some academic memory clinics work solely or mainly as tertiary referral services, where the most complex patients are referred from secondary referral nonacademic services. Moreover, the greater availability of technology and facilities allows EPAD memory clinics a much more biomarker-oriented diagnostic workup not always representative of the workup of nonacademic clinics. To improve the generalizability of the results, such academic memory clinics will engage affiliated nonacademic clinics for patients' recruitment and management.

3.3. Study design

AMYPAD-DPMS is a phase 4, multicenter, prospective, interventional, randomized controlled study. The study design is tightly linked to clinical procedures. After the first clinical consultation, where MRI or CT is either already available or prescribed, study screening takes place with inclusion/exclusion criteria check and informed consent explanation and signature. The baseline visit will take place within 14 days of screening. Here, patients are stratified into the three syndromic groups of SCD+, MCI, and dementia possibly due to AD and randomized soon thereafter into the three study arms (Fig. 3) using permuted blocks to assure that each arm is balanced to the syndromic groups such that each arm will include 100 SCD+, 100 MCI, and 100 dementia patients.

- ARM1 patients will undergo amyloid-PET early in the diagnostic workup (within 4 weeks from baseline), and the examination results are provided to the managing physician who will either order additional diagnostic tests or disclose diagnosis and set up a management plan.
- ARM2 patients will undergo amyloid-PET late in the diagnostic workup (8 months after baseline), and the managing physician can start the diagnostic workup either ordering other diagnostic tests or disclosing diagnosis and initiate a management plan according to usual local practices.
- In ARM3, the managing physician will be free to order amyloid-PET whenever he/she will feel fit, if at all. Here, amyloid-PET will be just yet another diagnostic examination available to the managing physician in addition to the usual armamentarium.

At the end of month 3 from baseline, the steps of the clinical workup carried out so far will be recorded into the study eCRF (electronic case report form), including syndromic and etiologic diagnoses, diagnostic confidence, likelihood that the symptoms are due to AD, and management plan all made by the managing physicians. At this point in time, the managing physician will have 3 more months to complete the diagnostic workup, disclose diagnosis, and set up a management plan (but we have considered the possibility that this may exceptionally not be the case). At the end of months 6 and 13 from baseline, the steps of the clinical workup will again be recorded into the study eCRF, together with health economics and patient-centered outcomes (Table 3). ARM1 patients will be invited to a second amyloid-PET scan that will take place 18 months after the first one and will contribute to the exploratory outcome of disease modeling central to the AMYPAD-PNHS study.

Although the meaning of ARM1 and ARM2 is relatively straightforward, ARM3 deserves specific discussion. A survey in 37 academic memory clinics of the European

Table 1
Major inclusion and exclusion criteria

Inclusion criteria: To be enrolled in the study, patients must meet all the following criteria.

- The patient can be of any sex, gender, race, or ethnicity.
- The patient must have a complaint (reported by the patient or by a caregiver) of cognitive problems that are considered by the managing physician to be possibly due to AD.
  - The patient must be entering a diagnostic assessment for the cognitive complaint.
  - The managing physician must feel that knowledge of the patient's brain amyloid status may increase diagnostic confidence and alter diagnosis and management.
  - In some centers, the patient may receive diagnostic workup before being screened for this study. These patients can be enrolled in the study; however, if they are assigned to the early amyloid-PET arm, the results of that workup must not be made available to the managing physician before the managing physician reviews the results of the amyloid-PET scan.
- The patient must satisfy the diagnostic criteria for one of the following (see Table 3): SCD-Plus, MCI, and dementia where AD is in the differential diagnosis.
- The patient has undergone a dementia blood workup or will have one before amyloid-PET.
- The patient has an MRI and/or CT scan (not older than 12 months) or will undergo one before amyloid-PET.
- The patient can complete all clinical visits according to the protocol.
- The patient can tolerate a 20-minute amyloid-PET scan.
- The patient (or a legal representative) provides informed consent for study participation and data source verification. In case the patient is randomized to the early amyloid-PET arm, a new informed consent should be signed before the second imaging session.
- If the patient has dementia, a study partner is available for the duration of the protocol.
- The patient wants to know the amyloid-PET result.

Exclusion criteria: Patients must be excluded from participating in this study if they meet any of the following criteria.

- The patient has another confirmed condition that can fully account for the cognitive impairment (neuroinflammatory, neuroinfective, or neurodegenerative disease; multiple sclerosis; genetic disorders; HIV; brain injuries; neurosurgery after-effects; major depressive episode; schizoaffective disorder; delusional disorder; delirium).
- The patient comes to observation for reasons other than diagnosis (disability assessment for social aids, cognitive assessment for driving license, etc.).
- The patient had a previous amyloid-β imaging scan and/or has had other AD biomarker workup (fluorodeoxyglucose [FDG]-PET and/or cerebrospinal fluid analysis) before screening. In some centers, the patient may receive a diagnostic workup before screening. These patients can be enrolled if the investigator is blind to the results until after randomization or (for patients in the early amyloid-PET arm) until after reviewing the results of amyloid-PET imaging.
- The patient has a life-threatening unstable medical disease or psychiatric condition that could lead to difficulty in complying with the protocol.
- The patient is currently receiving an investigational pharmaceutical product or has participated in a clinical trial with an investigational pharmaceutical product within 30 days before screening and/or was administered a radiopharmaceutical within 10 radioactive half-lives before study drug administration in this study.
- The patient is a woman who is pregnant, planning to become pregnant, or lactating.

Abbreviations: AD, Alzheimer's disease; PET, positron emission tomography; MCI, mild cognitive impairment; SCD, subjective cognitive decline.

Alzheimer's Disease Consortium (EADC) found that 60% of dementia specialists feel very or extremely comfortable to deliver a diagnosis of prodromal AD (or MCI due to AD) on the basis of standard assessment and amyloid-PET alone, while this proportion increases to 75% if also medial temporal atrophy on MRI or cortical hypometabolism on FDG-PET is present [42]. However, data are not available on the use of amyloid-PET in realistic settings with no budgetary or reimbursement constraints. ARM3 will allow the exploration of spontaneous and unrestricted ordering of amyloid-PET as well as to assess the dynamic change that might come with increasing familiarity with the examination over the 3-year lifetime of the trial.

3.4. Endpoints

The primary endpoint is to test the hypothesis that the proportion of patients for whom the managing physician reaches an etiologic diagnosis with very high confidence (≥90%) at 3 months after baseline is higher for patients who underwent amyloid-PET imaging shortly after baseline (ARM1) than for patients who have not yet undergone amyloid-PET imaging (ARM2). Diagnostic confidence will be rated by the managing physician using a visual analogue scale ranging from 0% to 100%. A diagnostic confidence of 90% is operationalized as an intermediate level between that of the pathological diagnostic gold standard (100%) and the nonbiomarker-assisted NINCDS-ADRDA probable AD diagnosis (80%). The primary endpoint does not directly encompass patient's quality of life or health-related outcomes. We assume that physician's high diagnostic confidence based on valid biomarkers is a proxy of accurate diagnosis, and that this, in turn, is associated with better quality of life and health-related outcomes. Although often undemonstrated, similar assumptions are frequent in diagnostic studies, due to the exceedingly complex and expensive implementation of clinical utility trials. Secondary and exploratory endpoints are listed in Table 3.

3.5. Amyloid-PET result disclosure to patients with SCD+

'The disclosure of amyloid-PET results to patients with MCI and dementia will follow the disclosure

Table 2
Inclusion and exclusion criteria specific to SCD+, MCI, and dementia where AD is in the differential diagnosis

SCD+ (modified from SCD-I Working Group criteria [17])
Inclusion criteria for SCD+
- Age between 60 and 85 years.
- The patient has perceived a decline in memory over time.
- The onset of the SCD is within the previous 5 years and the duration is >6 months.
- The Mini–Mental State Examination score is 27 to 30 out of 30 (MMSE score ≥ 27 is the optimal cutoff in terms of accuracy in detecting cognitive dysfunction; sensitivity: 0.89; specificity: 0.91; overall classification rate: 90% [40]).
- The clinical examination and neuropsychological assessment exclude MCI.
- Cognitive decline has been confirmed by an informant.
- The patient (or caregiver) has expressed concerns (worries) about the cognitive symptoms.
- Consultation has been actively requested by the patient or an informant.

Exclusion criteria for SCD+
- Current or past psychiatric disorders according to ICD 10 (including major depression, anxiety disorder, substance-related disorders, schizophrenia, bipolar disorder, adult ADHD, posttraumatic stress disorder). However, a depressive episode, an anxiety disorder, or a substance-related disorder that occurred >5 years earlier and in no temporal association with the onset of SCD is not a criterion for exclusion.
- Current or past history of a neurologic disease with known potential impact on cognition.
- MRI lesions that would not be consistent with a diagnosis of AD.
- Current use of medication with known effect on cognition, including sedatives and drugs with anticholinergic effect, if the clinician believes that the use of those drugs is the cause of cognitive impairment.

MCI (NIA-AA [33])
Inclusion criteria for MCI
- Age between 50 and 85 years.
- Concern regarding a change in cognition, as expressed by the patient, a proxy, or a physician.
- Impairment in one or more cognitive domains, as defined by neuropsychological test scores ≥1.5 SD below the age- and education-specific mean.
- Preservation of independence in functional abilities.
- No dementia.

Exclusion criteria for MCI
- Same as those of Table 1.

Dementia where AD is in the differential diagnosis (NIA-AA [34])
Inclusion criteria for probable AD dementia
- Age between 50 and 85 years.
- Insidious onset.
- Clear-cut history of worsening of cognition by report or observation.
- The initial and most prominent cognitive deficits are evident on history and examination.
- Presentation can be amnestic or nonamnestic (language, visuospatial, executive function, etc).
- The diagnosis of probable AD dementia should not apply when there is evidence of substantial concomitant cerebrovascular disease, dementia with Lewy bodies, behavioral variant of frontotemporal dementia, semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia, evidence for another concurrent, active neurological disease, or non-neurological medical comorbidity, or use of medication that could have a substantial effect on cognition.

Inclusion criteria for possible AD dementia
- Age between 50 and 85 years.
- Atypical course (either a sudden onset of cognitive impairment or insufficient historical details or objective cognitive documentation of progressive decline).

Exclusion criteria for probable and possible AD dementia
- Same as those of Table 1.

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; SCD, subjective cognitive decline; NIA-AA, National Institute on Aging and Alzheimer's Association.

NOTE. We applied different entry ages for SCD+, and MCI and dementia patients. As to SCD+, the entry age was set at 60 years, consistently with the SCD-I Working Group criteria for SCD+, to limit the prevalence of psychiatric cases (SCD at younger ages is enriched with persons with psychiatric conditions, whereas at older ages is enriched with neurodegenerative conditions) [17]. As to MCI and dementia, the entry age was set at 50 years to assess the clinical utility of amyloid-PET also in early-onset patients with objective cognitive impairment (and thus probable underlying neurodegenerative conditions).

protocols in place in the participating memory clinics. Importantly, the specialists' perception of the utility of amyloid-PET is remarkably homogenous across the memory clinics of the EADC, of which the AMYPAD-DPMS participating clinics are part [42]. Much more uncertain is the disclosure of amyloid-PET results to patients with SCD+. Indeed, the role of amyloid in the pathophysiological cascade ultimately leading to dementia is still unclear: prevalence of amyloid pathology in cognitively unimpaired people varies from 10% (50 years) to 44% (90 years) [38], and many will die without overt symptoms of AD. The recent National Institute on Aging and Alzheimer's Association criteria labels cognitively unimpaired persons with isolated amyloidosis as "Alzheimer's pathologic change" [35], a somewhat intermediate stance. Whatever the pathophysiology and lexicon, brain amyloidosis is undeniably a powerful risk factor for adverse cognitive outcomes.

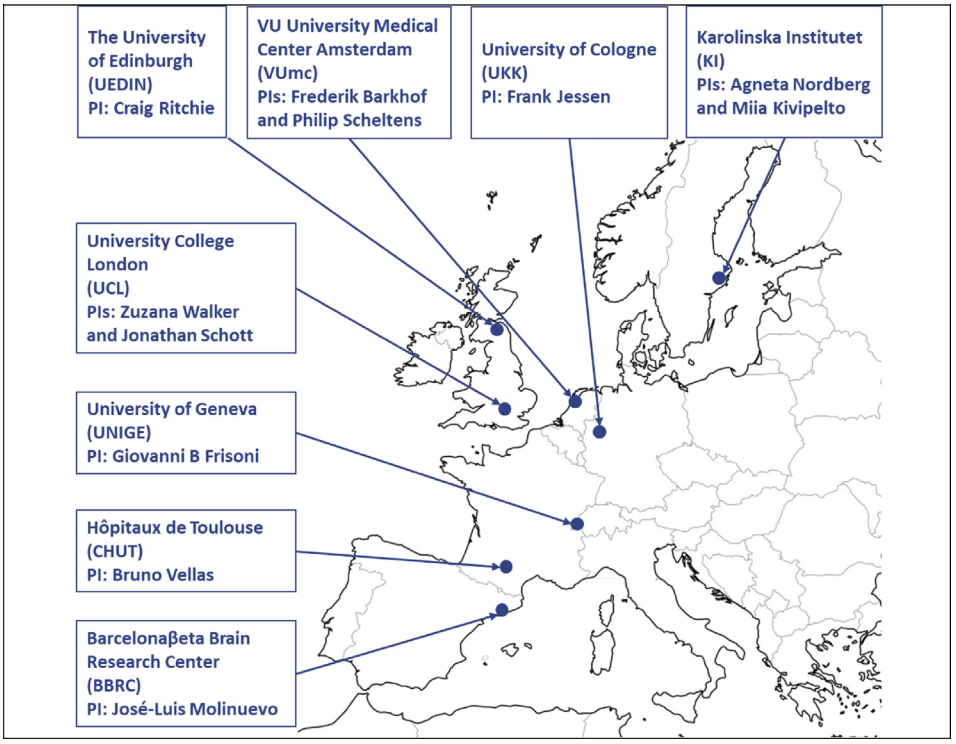

Fig. 2. Participating memory clinics.

The AMYPAD-DPMS consortium acknowledges that the desirability and usefulness of the communication of risk to patients with SCD+ are far from clear and are subject to several personal, clinical, social, and cultural modulating factors. According to the inclusion criteria, only patients who want to know their amyloid-PET result will be enrolled. We assume that this criterion allows to generalize our results to the clinical practice of memory clinics, where patients proactively seek medical help. Indeed, although there may be exceptions, we assume that these patients expect to undergo medical examinations and wish to know their results. The consortium agreed that in patients with SCD+, although formulating an etiological diagnosis is not appropriate in the routine clinical practice, the managing physicians will be asked to express their opinion on SCD being due to AD; amyloid-PET can be used for risk profiling; the disclosure of the result of amyloid-PET should be in terms of increased or decreased risk of AD dementia; disclosure is recommended and should follow guidelines adapted from those used in the A4 trial [43] (Tables S2 and S3 in Supplementary Material). Recent evidence suggests that the disclosure of the amyloid status in cognitively unimpaired patients is associated with a low risk of psychological harm [44], and that the prognostic uncertainty of amyloid-PET is correctly understood by two-thirds of patients [45]. The information delivered by the managing physician to each SCD+ participant will be recorded, based on the items listed in our guidelines. In exceptional cases, it is possible not to disclose (e.g., a patient changes her/his mind during the study, or the managing physician does not consider it appropriate anymore). These cases will be documented and justified but will not be removed from the study (consistently with the intention-to-treat approach: we include in our analyses every subject randomized according to randomized treatment assignment). Assuming that the physicians' beliefs on the pathophysiological role of amyloid in neurodegenerative diseases [46] can affect the disclosure of amyloid-associated risk, the managing physicians' beliefs will be recorded as well by asking them to fill in a questionnaire.

3.6. Statistics

For each of the three syndromic groups, the difference between ARM1 and ARM2 in the proportion of patients with a diagnostic confidence $\geq$90% at 3 months will be evaluated with a χ^2 test with overall significance level of 5%. A Bonferroni correction will be applied to the stratum-specific evaluation to control for family-wise type I error rate at 5%. The statistical evaluation will achieve a power of 80% when the assumed difference is 25% and not more than 10% of the patients withdraw before the endpoint is reached. Heterogeneity with respect to the estimated difference between arms will be examined with Breslow-Day test of homogeneity. If heterogeneity is significant, it will be accounted for in the statistical procedures.

Fig. 3. Design. Abbreviations: AMYPAD-DPMS, Amyloid Imaging to Prevent Alzheimer's Disease–Diagnostic and Patient Management Study; CSF, cerebrospinal fluid; Dx, diagnosis; T, time point; V, visit; eCRF, electronic case report form; QoL, quality of life; SCD+, subjective cognitive decline plus. We acknowledge that in some participating clinics, an extensive biomarker workup (e.g., CSF) is done on the first visit, before the patient can be screened for AMYPAD-DPMS. We stipulate that these patients can be enrolled in the study, but, if assigned to ARM1, the results of that workup will not be made available to the managing physician before they will be informed of the amyloid-PET result.

The secondary diagnosis and diagnostic confidence outcomes are time-to-event measures, and differences between arms will be tested with the log-rank test. Dropout is accounted for by censoring at the time of the last study visit. Differences between arms in the diagnostic/therapeutic management, health economics, and patient-centered outcomes will be evaluated with a χ^2 test, *t*-test, or Mann-Whitney test whichever is appropriate. Longitudinal trends of the diagnostic/therapeutic management, health economics, and patient-centered outcomes will be studied by mixed effects analyses that allow for patient-specific and center-specific effects and that can be applied to interval, dichotomous, and count data. Point estimates will be presented together with 95% Wald confidence intervals. Bonferroni corrections for multiple testing will be applied when appropriate. Data will be censored after a major protocol deviation.

4. Expected results and impact

The major impact of AMYPAD-DPMS will consist in providing empirical evidence on the effect of amyloid-PET on diagnostic thinking, management outcomes, patient outcomes, and use of health care resources. The evidence will be used by physicians for more informed management decisions and by health care payers for decisions about reimbursement of amyloid-PET. This will be a unique contribution in that the only other large study on this topic, IDEAS in the USA, differs under several key aspects. IDEAS is a naturalistic study where 18,448 Medicare patients satisfying the AIT appropriate use criteria [11,12] recruited from specialty practices undergo amyloid-PET. Outcomes are change in a management composite endpoint and reduction in hospitalization and emergency department visits. Controls are selected based on "propensity matching" of patients with similar sociodemographic and clinical features who did not undergo amyloid-PET.

The randomized and controlled design of AMYPAD-DPMS will provide stronger evidence on the difference of primary and secondary outcomes between patients undergoing early or late amyloid-PET. AMYPAD-DPMS will not limit amyloid-PET to patients considered appropriate by the AIT. Indeed, preliminary evidence indicates an impact of amyloid-PET on change of diagnosis and management also in AIT-inappropriate patients [47]. The inclusion of patients with SCD+, clearly an AIT-inappropriate group, will allow to investigate the use and interpretation of amyloid-PET in these patients increasingly requiring medical opinion in memory clinics and of increasing interest for intervention trials, who will pose a major challenge for the near future. Indeed, patients with SCD have different needs than those with cognitive/functional impairment, and recent efforts are moving toward the creation of the so-called "brain health clinics/services" [48], clinical facilities with specific aims and missions

Table 3
Secondary [A] and exploratory [B] endpoints

[A] Secondary endpoints

Diagnosis and diagnostic confidence

To assess the impact of amyloid-PET imaging on other diagnosis-related metrics:

- Time to communicate to the patient an etiologic diagnosis with very high confidence (≥90%);
- Changes in the managing physician's etiologic diagnosis over time;
- Changes in the managing physician's diagnostic confidence over time;
- The managing physician's estimate of the likelihood that the patient's symptoms are due to AD; and
- How the placement of amyloid-PET imaging in the clinical workup, when the managing physician is given free choice, changes over time.

Diagnostic/therapeutic management

To assess the impact of amyloid-PET imaging on patient management, including

- The number of patients randomized to disease-modifying drug or any other AD clinical trial at 6 months from baseline;
- Change or early adoption of programs and/or pharmacologic treatments aimed to delay the onset or progression of cognitive impairment; and
- Use of medical resources (including but not limited to diagnostic procedures, tests, programs, visits, and hospitalizations).

Health economics and patient-centered outcomes

To assess the impact of amyloid-PET imaging on

- Patient-related outcomes (cognition, anxiety, depression, coping skills, and quality of life);
- Cost of diagnostic workup to the etiologic diagnosis with very high confidence (≥90%); and
- The number of patients who are discharged from the memory center and the reason for discharge.

Methods for image quantitation

- To test the hypothesis that amyloid load is stable over 18 months.
- To develop standardized methods of image quantitation across the PET tracers (e.g., using the Centiloid scale [41]) to allow pooled analysis of [^{18}F] florbetaben and [^{18}F]flutemetamol scans across the AMYPAD program.

[B] Exploratory endpoints

- Impact of amyloid-PET according to different cognitive profiles (amnesic vs. nonamnesic).
- Impact of disclosing the amyloid status to patients with SCD+ on quality of life and patient-centered outcomes over time.
- Assessment of the utility of amyloid-PET staging and modeling approaches across diagnostic groups.
- Collection of evidence on the clinical utility of amyloid-PET over other biomarkers to contribute to outline a cost-effective diagnostic algorithm (for instance, a subsample of patients will undergo amyloid-PET before CSF if the latter is prescribed (ARM1), whereas others will undergo amyloid-PET after CSF if the latter is prescribed (ARM2). Therefore, we will be able to compare the relative incremental value of amyloid-PET over CSF markers and vice versa, and to assess whether and how the inclusion of CSF in the diagnostic workup affects the frequency of the subsequent prescription of amyloid-PET in ARM3).
- Assessment of whether and how the clinical utility and cost-effectiveness of amyloid-PET differ between academic and non-academic memory clinics by a posteriori stratified analyses (we can expect some differences among different centers in the use and interpretation of the amyloid-PET result depending on their level of experience).

Abbreviations: PET, positron emission tomography; AD, Alzheimer's disease; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; SCD, subjective cognitive decline.

The likelihood of AD (0–100%) corresponds to the physician's judgment that the patient's cognitive impairment (or concern, in SCD+) is due to AD. The treatment plan may include cognition-specific medications (AChEIs and/or memantine) and noncognition-specific medications (e.g., anxiolytics, hypnotics, antidepressants, antipsychotics, and anticonvulsants).

See e3.4 in Supplementary Material for further information about the tools used to assess "use of medical resources" and "patient-related outcomes."

dealing with healthy people and SCD. Data collected within AMYPAD-DPMS will provide unique evidence that brain health clinics/services will use to implement risk assessment and communication protocols. Finally, the design of ARM3 will allow to investigate the dynamics over time of specialists' diagnostic thinking when amyloid-PET is made available with no restriction. This will provide key information on the placement of a PET scan in the diagnostic algorithm, a key topic of interest to the European Medicines Agency and health technology assessment bodies.

One limitation of this study is that only some European countries are involved, and these differ for health systems, policies, and laws. These aspects may impact on some of our secondary endpoints (diagnostic/therapeutic management, and health economics and patient-centered outcomes) and prevent us from generalizing our results to all Europe. However, such differences will not impact on the primary endpoint (diagnostic confidence).

To conclude, in the validation process of diagnostic biomarkers, the impact of their use on patient's health outcomes and quality of life and cost-effectiveness outcomes is paramount to payers [49]. The focus of AMYPAD-DPMS on such outcomes will allow to collect structured and reliable information that will critically contribute to payers' reimbursement decisions.

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Supplementary data

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RESEARCH IN CONTEXT

1. Systematic review: Evidence on the amyloid-PET clinical utility is still limited: most of the studies published so far are only observational and lack proper study designs for a systematic and definitive assessment. Moreover, and most importantly, evidence on real-life effectiveness and cost-effectiveness in the absence of disease-modifying therapies is lacking. The Amyloid Imaging to Prevent Alzheimer's Disease–Diagnostic and Patient Management Study (AMYPAD-DPMS) is designed to fill this gap.
2. Interpretation: AMYPAD-DPMS will provide empirical evidence on the effect of amyloid-PET on diagnostic thinking, management outcomes, patient outcomes, and use of health care resources. Moreover, the randomized and controlled design of AMYPAD-DPMS will provide strong evidence on the difference of the outcomes between patients undergoing early and late amyloid-PET.
3. Future directions: AMYPAD-DPMS will allow to collect structured and reliable information that will be used by physicians for more informed management decision and will critically contribute to payers' amyloid-PET reimbursement decisions.

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