The Added Value of Quantitative Amyloid PET in Determining Alzheimer's Disease (AD) Dementia Risk: The Amypad Prognostic and Natural History Study

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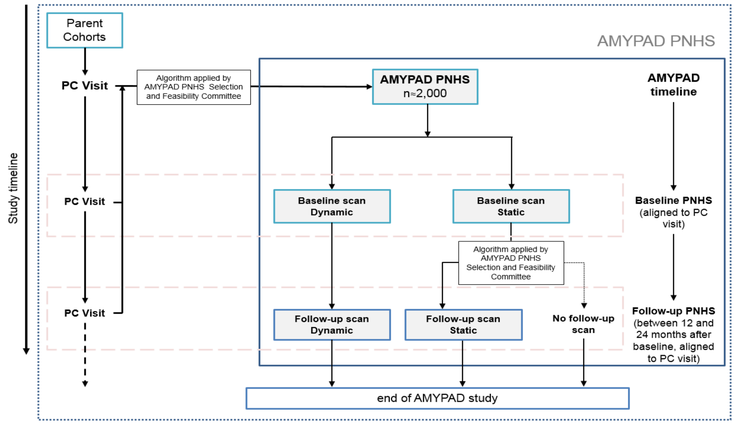
Background

Amyloid imaging by Positron Emission Tomography (PET) provides a unique opportunity to visualize the spatial distribution of amyloid-β (Aβ) plaques in the brain *in vivo*. Current research efforts place the accumulation of these plaques as the earliest detectable change in the path towards AD. With the shift in focus of clinical trials towards secondary prevention, identification of subjects at risk of developing AD dementia is crucial. However, these subjects' Aβ biomarkers may be around dichotomous abnormality cut-offs (so-called 'gray-zone') and quantitative methods play a crucial role.

The AMYPAD Prognostic and Natural History Study (AMYPAD-PNHS) focuses on such individuals and quantitatively estimates Aβ load from (static and dynamic) PET imaging to support longitudinal cohorts of cognitively unimpaired subjects in improving the chances of success for AD prevention trials.

AMYPAD PNHS Goal

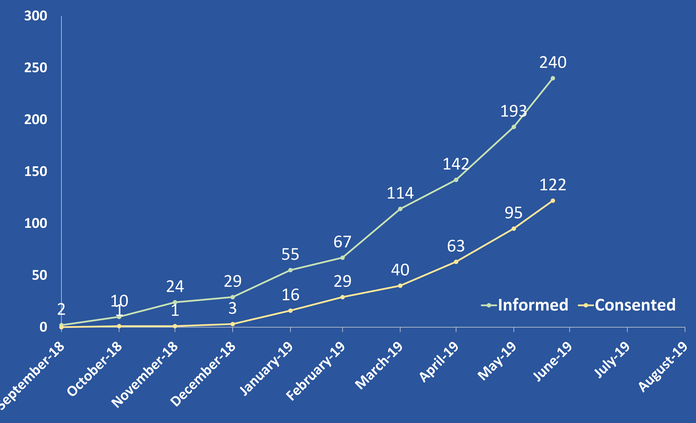
To predict progression within an AD risk probability spectrum (derived from four different dimensions: cognition, other biomarkers, traditional genetic and environmental risk factors and changes in these) based on quantitative amyloid PET



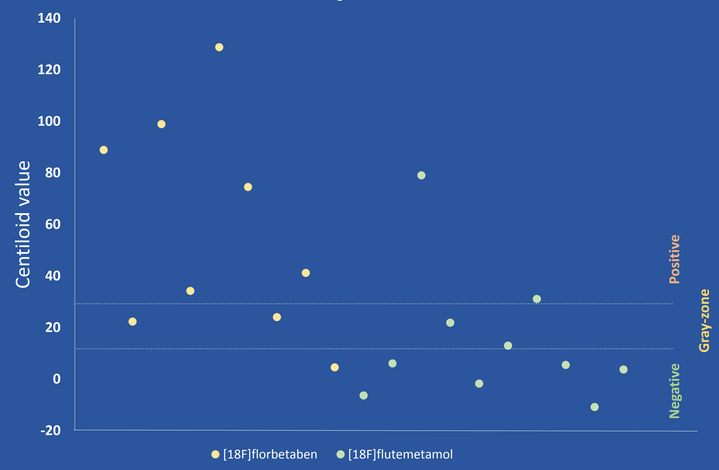
AMYPAD PNHS will enroll **2000 subjects**, of which **1000 will undergo a follow-up PET scan** 1-2 years after baseline.

The main outcomes are quantitative measurements of amyloid burden such as **SUVR, Centiloid and DVR**. The latter will be available from a large proportion of subjects, who will undergo *dynamic scanning*. This will allow a more accurate quantification of the pathology and a head-to-head comparison to the widely used SUVR in the context of early pathological identification.

AMYPAD PNHS currently **has** **5 active sites** and **122 participants** enrolled



Of 19 QC-ed and quantified scans, 7 are negative, 4 are gray-zone and 8 are positive*



* Salvado et al, Alzheimers Res Ther. 2019 Mar 21;11(1):27 **(negative < 10 CL; positive > 30 CL)**

Sites and Parent Cohorts

AMYPAD Sites will include **seven partner sites** and approximately **thirteen collaborating sites**.

In addition, the study will recruit from a variety of the parent cohorts (PCs) across Europe, including but not limited to **EPAD LCS, the Twin-cohort from EMIF-AD, ALFA+, FACEHBI, and others**. This will allow PNHS to complement ongoing efforts in the PCs by providing access to amyloid PET as an early biomarker, while being granted access to additional variables in order to model cross-biomarker relationships and their effects on disease progression. **Jointly, all projects can efficiently address their respective objectives** form a multi-model perspective without further burdening additional *de novo* research participants.

Recruitment and focus on gray-zone

As the study aims to better understand the earliest stages of AD, this involves **focusing on the beginning of the amyloid cascade, where individuals might have emerging pathology traditionally undetected by established standards**.

More specifically, AMYPAD PNHS aims to include not only **amyloid-positive participants (20%)**, but also those with **negative amyloid PET scans (20%)**, and those in a so-called **grey-zone of amyloid burden (60%)**, who e.g. have ambiguous or discordant CSF and PET amyloid status, or who are on the normal/abnormal boundary of quantitative amyloid load.

Expected Impact

Amyloid PET imaging holds great promises for a better understanding and phenotyping of preclinical and prodromal Alzheimer's disease. The project is expected to **contribute to determining**:

- The **added value of amyloid PET** in assessing AD dementia risk;
- The **natural history of amyloid accumulation** and its contribution to future cognitive decline;
- The **optimal methodology** to quantitatively assess amyloid burden and its accumulation;
- How **amyloid PET** can be **used for clinical trials** of secondary prevention

Academic partners **SMEs** **Industrial partners** **Patient Organization**

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