Current Status and Quantitative Results of the AMYPAD Prognostic and Natural History Study

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on behalf of the AMYPAD Consortium

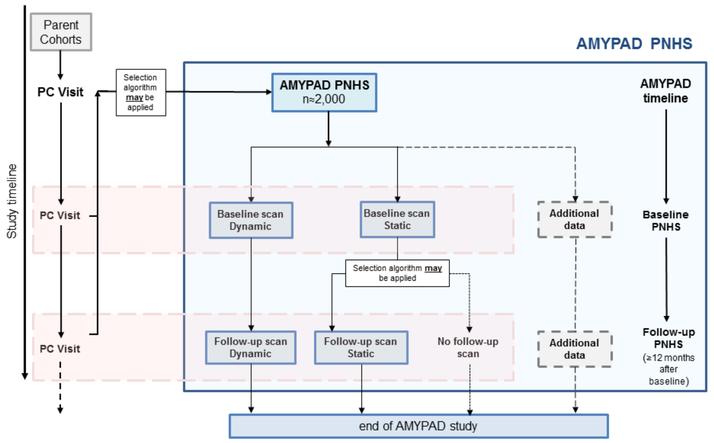
Background

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

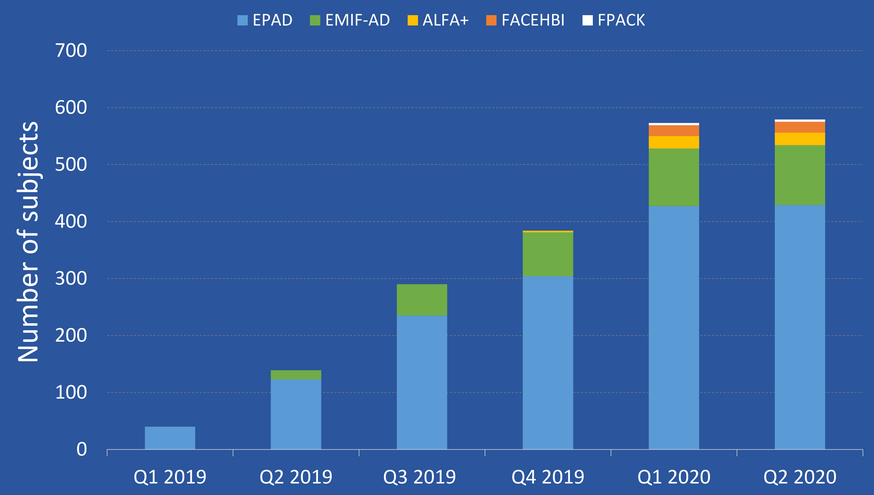
To predict progression within an AD risk probability spectrum (derived from four different dimensions: cognition, other biomarkers, traditional genetic and environmental risk factors and changes in these) based on quantitative amyloid PET



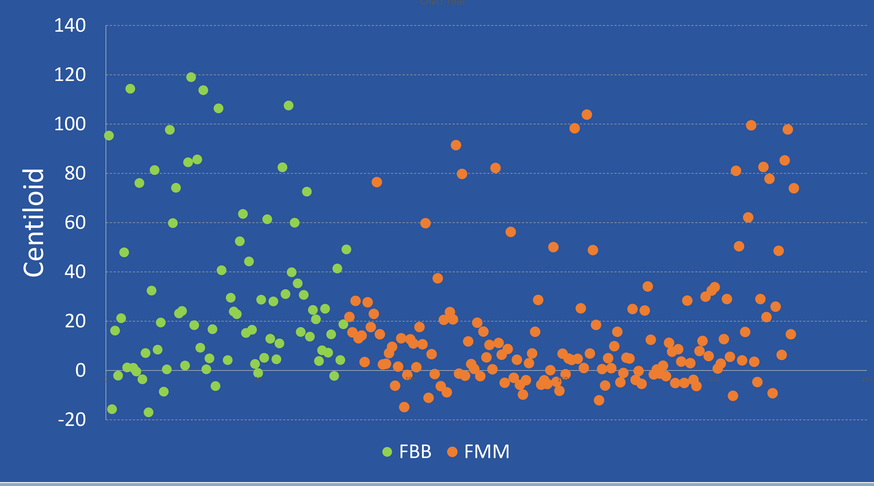
AMYPAD PNHS will enroll **2000 subjects**, of which **1000 will undergo a follow-up PET scan** at least 1 year after baseline. For some participants, additional cognitive data may be collected in parallel, should their Parent Cohort (PC) not provide the necessary data for analysis.

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 **has 17 active sites, 579 participants** enrolled and **421 scans** performed



Of 226 QC-ed and quantified scans, 51% are negative (CL<12), 32% are gray-zone and 16% are positive (CL≥50)



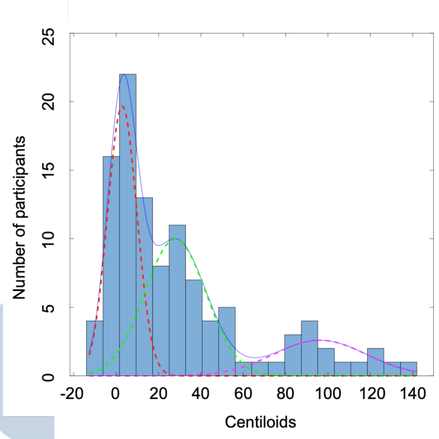
Sites and Parent Cohorts

AMYPAD Sites includes **seven partner sites** and **ten collaborating sites**.

In addition, the study recruits from a variety of PCs across Europe, including but not limited to **EPAD LCS, the Twin-cohort from EMIF-AD, ALFA+, FACEHBI, FPACK, 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 gray-zone definition

As the study aims to better understand the earliest stages of AD, 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.



Gaussian mixture modeling (GMM) of the distribution of Centiloid values was performed by fitting 3 Gaussian curves to the data. Subjects were categorized as **negative (CL<12)**; in the **gray-zone (12≤CL<50) or positive (CL≥50)** following the GMM results and previous literature [1,2].

References

[1] Salvadó G., et al, 2019

[2] Amadoru S.., et al, 2020

Academic partners | SMEs | Industrial partners | Patient Organization

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