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Integration of canonical biomarkers in the diagnosis of preclinical Alzheimer disease

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An estimated 55–60 million individuals have dementia globally and this number is expected to triple by 2050[1]. These figures emphasize the urgent need to identify effective dementia treatments; however, a major hindrance to the efficient deployment of dementia therapies in the general population is the lack of clinically validated diagnostic methods that use objective, disease-associated biomarkers. Alzheimer disease (AD) is the most common type of dementia and accounts for 60–80% of all cases. The two canonical pathologies observed in the AD brain are extracellular deposits of amyloid-β peptides, which form the backbone of prototypical senile plaques, and the intraneuronal accumulation of abnormal, hyperphosphorylated tau proteins, which aggregate into neurofibrillary tangles[2]. The current model of AD pathogenesis describes the appearance of brain pathologies several years before clinically measurable cognitive symptoms[3], suggesting that the detection of AD-associated biomarkers should be possible in cognitively unimpaired individuals with preclinical AD.

In the past 2 decades, technological innovations have permitted the detection of amyloid and tau aggregates in the brain of living individuals using PET. Furthermore, in 2016, a framework was published that stratified individuals on the basis of a combination of amyloid (A), tau (T), and neurodegeneration (N) biomarkers — an individual can be either positive or negative for each biomarker[4]. This originally research-oriented 'ATN' framework was designed to improve recruitment in clinical trials and was derived from the most recent criteria for the clinical definition of AD by the National Institute on Aging, the Alzheimer's Association and the AD International Working Group. The ATN framework has since proven efficient in research settings[7] and the next question is whether it can be applied to medical practice to diagnose individuals across the entire continuum of AD, and to assess risk of progression from preclinical AD to dementia. Indeed, individuals at the preclinical stage are the most likely to benefit from future preventative therapies. In a new study, Rik Ossenkoppele and colleagues[5] asked how well amyloid and tau PET could predict

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short-term progression to cognitive impairment in cognitively unimpaired individuals, thus bringing us closer to an answer to this important question.

The new study comprised 1,325 cognitively unimpaired participants, aged 57–86 years, drawn from seven population-based cohorts distributed worldwide[5]. Participants were monitored for progression to mild cognitive impairment (MCI) and dementia for up to 72 months. The A and T elements of the ATN framework were inferred from amyloid and tau PET data. The neurodegeneration criterion was not applied in this study because identifying neurodegeneration in individuals who are negative for both amyloid and tau (A^-T^-) is difficult. With this simplified matrix, 63.6% of participants in the study were A^-T^-, 24.8% were amyloid positive and tau negative (A^+T^-), and 2.5% were amyloid negative and tau positive (A^-T^+). Individuals who were A^+T^+ were further subdivided on the basis of whether the tangles were sequestered to the medial temporal lobe ($A^+T_{MTL}{}^+$; 4.2%) or spread through the temporal neocortex ($A^+T_{NEO\text{-}T}{}^+$; 4.9%), although no major differences in outcomes were noted between these two groups.

Ossenkoppele and colleagues[5] used Cox proportional-hazards models to investigate the risk of conversion from cognitively unimpaired to MCI and all-cause dementia in each of the groups. The A^+T^+ groups yielded higher hazard ratios than the A^-T^- group, indicating a higher risk of conversion in individuals who are A^+T^+. About half of the individuals in the A^+T^+ groups progressed to MCI and all-cause dementia during the observation period. The authors suggest that those who progressed to MCI or dementia in the $A^+T_{NEO\text{-}T}{}^+$ group could have been at a more advanced stage of disease, as they tended to have higher tau PET signals at baseline. These findings were accompanied by faster cognitive decline in the A^+T^+ groups than the A^-T^- group, as assessed by linear mixed-effect models on several outcome measures, including Mini-Mental State Examination and the modified preclinical Alzheimer cognitive composite 5 and its subcomponents — delayed episodic memory, timed executive function, and semantic memory. The $A^+T_{NEO\text{-}T}{}^+$ group showed the fastest decline overall. The A^+T^- group had increased risk of progression to MCI and speed of cognitive decline compared with the A^-T^- group; however, this increase was much smaller than for the A^+T^+ groups. All findings were independent of age.

The results for the A^+T^- group are in line with the long-standing absence of correlation between amyloid burden and clinical trajectory. These findings contrast with those previously reported for the Australian Imaging Biomarkers and Lifestyle study[6], which indicated that high amyloid loads were associated with a faster trajectory of cognitive decline. However, the latter study did not integrate tau PET but relied solely on amyloid PET data. The study by Ossenkoppele and colleagues[5] strongly suggests that tau positivity on PET is a potent predictor and driver of the risk of progressive cognitive decline and dementia. This finding concurs with the results of another study published in 2022, of four independent population-based cohorts that overlapped with the Australian Imaging Biomarkers and Lifestyle cohort[7]. Surprisingly, age as a covariate had a minimal impact on the disease trajectory and progression risk. Although the seven cohorts were geographically diverse, they were not racially or ethnically diverse. This issue will need to be addressed in future studies because race and ethnicity are thought to affect amyloid PET signal[8].

The main limitation of the study by Ossenkoppele and colleagues is its large attrition rate, which is an issue in most multiyear observational studies. Furthermore, the predictive model did not include a marker of neurodegeneration or known risk factors for AD, for example, *APOE ε4* genotype These factors, along with amyloid and tau, could soon be derived from peripheral biofluids such as blood and saliva, which could help keep diagnostic tests affordable when deployed in the general population. Thus, realistic operationalization of the ATN framework could be combined with additional biomarkers such as inflammatory markers, and markers of genetic and environmental risk factors[9] to develop better composite diagnostic scales.

Nonetheless, the findings of the study by Ossenkoppele and colleagues support the concept that an A^+T^+ PET result is a strong indicator of preclinical AD. A^+T^+ PET was associated with a 50% risk of progression to MCI or dementia within 4 years and was a predictor of faster cognitive decline. These new findings advance our ability to predict whether cognitively unimpaired individuals are likely to progress to AD within 3–4 years. Furthermore, our professional opinion is that the integration of other known risk factors and markers of neurodegeneration would enhance the precision of these predictions. These predictions could form part of a personalized medicine paradigm to help guide the prescription of future preventative interventions, such as the upcoming anti-amyloid-β therapies[10].

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Findings from a worldwide cohort of cognitively unimpaired individuals demonstrate that the presence of two canonical Alzheimer disease (AD) biomarkers — amyloid and tau — can reliably predict progression to mild cognitive impairment in the short-term. The results support the use of these biomarkers to diagnose preclinical AD in a clinical setting.

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