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## Alzheimer's Disease Normative Cerebrospinal Fluid Biomarkers Validated in PET Amyloid- $\beta$ Characterized Subjects from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study

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**Abstract:** Background: The cerebrospinal fluid (CSF) amyloid- $\beta$  ( $A\beta$ )<sub>1-42</sub>, total-tau (T-tau), and phosphorylated-tau (P-tau<sub>181P</sub>) profile has been established as a valuable biomarker for Alzheimer's disease (AD). Objective: The current study aimed to determine CSF biomarker cut-points using positron emission tomography (PET)  $A\beta$  imaging screened subjects from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging, as well as correlate CSF analyte cut-points across a range of PET  $A\beta$  amyloid ligands. Methods:  $A\beta$  pathology was determined by PET imaging, utilizing <sup>11</sup>C-Pittsburgh Compound B, <sup>18</sup>F-flutemetamol, or <sup>18</sup>F-florbetapir, in 157 AIBL participants who also underwent CSF collection. Using an INNOTEST assay, cut-points were established ( $A\beta$ <sub>1-42</sub> >544 ng/L, T-tau <407 ng/L, and P-tau<sub>181P</sub> <78 ng/L) employing a rank based method to define a "positive" CSF in the sub-cohort of amyloid-PET negative healthy participants (n=97), and compared with the presence of PET demonstrated AD pathology. Results: CSF  $A\beta$ <sub>1-42</sub> was the strongest individual biomarker, detecting cognitively impaired PET positive mild cognitive impairment (MCI)/AD with 85% sensitivity and 91% specificity. The ratio of P-tau<sub>181P</sub> or T-tau to  $A\beta$ <sub>1-42</sub> provided greater accuracy, predicting MCI/AD with  $A\beta$  pathology with 92% sensitivity and specificity. Cross-validated accuracy, using all three biomarkers or the ratio of P-tau or T-tau to  $A\beta$ <sub>1-42</sub> to predict MCI/AD, reached 92% sensitivity and specificity. Conclusions: CSF  $A\beta$ <sub>1-42</sub> levels and analyte combination ratios demonstrated very high correlation with PET  $A\beta$  imaging. Our study offers additional support for CSF biomarkers in the early and accurate detection of AD pathology, including enrichment of patient cohorts for treatment trials even at the pre-symptomatic stage.

**Keywords:** Alzheimer's disease, amyloid- $\beta$ , cerebrospinal fluid biomarkers, positron emission tomography  $A\beta$  imaging, tau

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