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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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**Authors:** Li, Qiao-Xin<sup>a</sup> | Villemagne, Victor L.<sup>a; b</sup> | Doecker, James D.<sup>c</sup> | Rembach, Alan<sup>a; †</sup> | Sarros, Shannon<sup>a</sup> | Varghese, Shiji<sup>a</sup> | McGlade, Amelia<sup>a</sup> | Laughton, Katrina M.<sup>a</sup> | Pertile, Kelly K.<sup>a</sup> | Fowler, Christopher J.<sup>a</sup> | Rumble, Rebecca L.<sup>a</sup> | Trounson, Brett O.<sup>a</sup> | Taddei, Kevin<sup>e; f</sup> | Rainey-Smith, Stephanie R.<sup>e; f</sup> | Laws, Simon M.<sup>e; f</sup> | Robertson, Joanne S.<sup>a</sup> | Evered, Lisbeth A.<sup>g</sup> | Silbert, Brendan<sup>g</sup> | Ellis, Kathryn A.<sup>a; h</sup> | Rowe, Christopher C.<sup>a; b</sup> | Macaulay, S. Lance<sup>i</sup> | Darby, David<sup>a</sup> | Martins, Ralph N.<sup>e; f; j</sup> | Ames, David<sup>h; k</sup> | Masters, Colin L.<sup>a</sup> | Collins, Steven<sup>a; d; \*</sup> | and for the AIBL Research Group<sup>l</sup>

**Affiliations:** [a] Florey Institute of Neuroscience and Mental Health, The University of Melbourne, VIC, Australia | [b] Department of Nuclear Medicine and Centre for PET, Austin Health, Heidelberg, VIC, Australia | [c] CSIRO Digital Productivity/Australian e-Health Research Centre and Cooperative Research Centre

for Mental Health, Brisbane, QLD, Australia | [d] Department of Pathology, The University of Melbourne, Parkville, Australia | [e] Centre of Excellence for Alzheimer's Disease Research & Care, School of Medical Sciences, Edith Cowan University, Joondalup, Western Australia, Australia | [f] Sir James McCusker Alzheimer's Disease Research Unit (Hollywood Private Hospital), Perth, WA, Australia | [g] Centre for Anaesthesia and Cognitive Function, Department of Anaesthesia, and Department of Surgery, St. Vincent's Hospital, The University of Melbourne, VIC, Australia | [h] The University of Melbourne Academic Unit for Psychiatry of Old Age, St George's Hospital, Kew, VIC, Australia | [i] CSIRO Food and Nutrition Flagship, Parkville, VIC, Australia | [j] School of Psychiatry and Clinical Neurosciences, University of Western Australia, Perth, Western Australia, Australia | [k] National Ageing Research Institute, Parkville, VIC, Australia | [l] <http://aibl.csiro.au/>

**Correspondence:** [\*] Correspondence to: Steven Collins, MD, Department of Pathology, The University of Melbourne, Parkville 3010, Australia. Tel.: +61 3 9035 7682; Fax: +61 3 9035 3105; [stevenjc@unimelb.edu.au](mailto:stevenjc@unimelb.edu.au)

**Note:** [†] Unexpectedly deceased 20 November 2014.

**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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