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

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

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

Note: [†] Unexpectedly deceased 20 November 2014.

Abstract: Background: The cerebrospinal fluid (CSF) amyloid-⊠ (A⊠)1-42, total-tau (T-tau), and phosphorylated-tau (P-tau181P) 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⊠ 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⊠ amyloid ligands. Methods: A⊠ pathology was determined by PET imaging, utilizing 11C-Pittsburgh Compound B, 18F-flutemetamol, or 18F-florbetapir, in 157 AIBL participants who also underwent CSF collection. Using an INNOTEST assay, cut-points were established (A⊠1-42 >544ng/L, T-tau <407ng/L, and P-tau181P <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⊠1-42 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-tau181P or T-tau to A⊠1-42 provided greater accuracy, predicting MCI/AD with A⊠ pathology with ⊠92% sensitivity and specificity. Cross-validated accuracy, using all three biomarkers or the ratio of P-tau or T-tau to A⊠1-42 to predict MCI/AD, reached ⊠92% sensitivity and specificity. Conclusions: CSF A⊠1-42 levels and analyte combination ratios demonstrated very high correlation with PET A⊠ 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-⊠, cerebrospinal fluid biomarkers, positron emission tomography A⊠ imaging, tau

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