# Shorts on Standards—Establishing cutoffs, reference ranges for biofluid biomarkers in Alzheimer's disease: Reference materials and reference measurement procedures

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October 2018—The newly developed National Institute on Aging and Alzheimer's Association (NIA-AA) research framework uses a biological definition of Alzheimer's disease.[1] This framework has increased focus on biofluid biomarkers, especially because the measurement of cerebrospinal fluid amyloid beta peptide 42 (Aβ42) (or Aβ 42/40 ratio), phosphorylated tau protein (p-tau), and total tau proteins (T-tau) are included in the definition.[1] The field of AD biofluid biomarkers is rapidly evolving. For example, CSF neurofilament light (NfL) is associated with AD neurodegeneration and may be a better CSF marker compared with T-tau. There has also been tremendous progress in the development of plasma biomarkers (i.e. Aβ42 or Aβ 42/40 ratio, NfL, and p-tau) that are associated with AD pathophysiological processes. These biofluid biomarkers hold promise as clinically useful screening, diagnostic, and prognostic tests for AD. For example, these plasma biomarkers may be used as an initial screen for abnormal amyloid deposition or neurodegeneration, with follow-up CSF biomarker testing and/or neuroimaging for clinical confirmation.

There are challenges, however, in implementing these biofluid biomarkers in clinical practice. One challenge is the lack of cutoff levels and reference ranges for routine clinical use and the lack of harmonization and standardization among different methods and laboratories. The Alzheimer's Association thus established an international quality control program for CSF biomarkers in 2009. This program raised awareness of method and lab differences and the lack of harmonized methods, which can be overcome through the development of reference measurement procedures, the use of certified reference materials (CRMs), and the establishment of a traceability chain.[2]

To this end, reference measurement procedures for CSF Aβ42 and/or the Aβ 42/40 ratio were developed. The International Federation of Clinical Chemistry and Laboratory Medicine developed a working group that has produced CRMs that are commutable for CSF Aβ42 assays. Assay manufacturers can use the CRM to calibrate their assays, which should improve concordance of measurement results between different CSF Aβ42 assays and will make it possible to establish a global cutoff.[2]

Despite this success, there remains a need to develop reference measurement procedures and CRMs for other CSF and plasma biomarkers (e.g. NfL and p-tau). Availability of these reference procedures and CRMs will help to harmonize methods for establishing global cutoffs and reference ranges of additional biofluid biomarkers for screening, diagnosis, and prognosis of AD.

1. Jack CR Jr., Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement.* 2018;14(4):535–562.
2. Andreasson U, Kuhlmann J, Pannee J, et al. Commutability of the certified reference materials for the standardization of β-amyloid 1–42 assay in human

cerebrospinal fluid: lessons for tau and β-amyloid 1–40 measurements. *Clin Chem Lab Med.* 2018; doi:10.1515/cclm-2018-0147.

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