CSF biomarker variability in the Alzheimer’s Association quality control program

S. Persson, U. Andreasson, H. Zetterberg, and K. Blennow
Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology at Sahlgrenska Academy, University of Gothenburg

Background
The Alzheimer’s Association Quality Control (AAQC) program for biomarkers in cerebrospinal fluid (CSF) was started in 2009 as an attempt to monitor site-to-site variation, harmonize levels and pave the way for uniform cut-off levels for measurement of the CSF biomarkers amyloid-β 1-42 (Aβ1-42), total-tau (T-tau), and phosphorylated-tau (P-tau) that are used for Alzheimer’s disease (AD) research and patient management.

Method
The AAQC program consist of three rounds each year with three samples of pooled CSF (one longitudinal and two unique) prepared at the Clinical Neurochemistry Laboratory at the University of Gothenburg, Sweden. The samples are analyzed by participating laboratories for T-tau, P-tau, and Aβ1-42. Up to now there have been 16 rounds of this program.

Data from the unique samples from the two last rounds of the program were used to explore the between laboratory difference between the old and new (with ready to use calibrators (RTU)) INNOTEST (Fujirebio). The old and new (validated) MSD 6E10 multiplex kit from Mesoscale Discovery (MSD) was examined using data from the Longitudinal sample from the last ten rounds. Since all participant’s using this kit switch to the validated kit in round 12 we have compared all results from round 7 to 11 with all results from round 12-16.

Data form the unique samples from the last round was used to explore the between laboratory difference between newly introduced ELISA kits from EUROIMMUNE/ADx and the novel not yet commercial available fully automated Elecsys assay from Roche.

Results
The between laboratory CV for the old INNOTEST T-tau ELISA kits were 15-25% with 19% mean CV and 7-22% with 15% mean CV between the laboratories using the new RTU INNOTEST T-tau ELISA kits.

The difference in CVs between the laboratories using the old INNOTEST β-amyloid 1-42 ELISA kits were 15-26% with a 20% mean CV and 9-27% with mean CV 16% between the laboratories using the new RTU INNOTEST β-amyloid 1-42 ELISA.

The between laboratory CVs for newly introduced ELISA kits from EUROIMMUNE/ADx were: for T-tau ELISA 6% and 21%, for Aβ1-42 19% and 57%, and for Aβ1-40 23% and 46%.

Data form the novel not yet commercial available fully automated Elecsys assay from Roche showed between laboratory CVs of 2.0% and 2.9%.

Conclusions
• The overall variability of CSF biomarker measurements is still too high to allow assignment of universal cut-off values.
• The introduction of validated MSD and ready to use Fujirebio kits show some improvement in performance.
• The newly introduced EUROIMMUNE/ADx ELISA show large variability, which may improve as laboratories get more experience with this assay.
• The new fully automated Roche Elecsys assay show very low variability. Data on batch-to-batch variability will be available in future round of the AAQC.

Take home message
The high between-lab variability for the AD biomarkers still remains a problem. However, introduction new fully automated system is in the horizon.