The Alzheimer’s Association quality control program

Ulf Andreasson
QC program facts

- Initiated 2009 and 98 laboratories are now listed in the database.
- Three rounds/year with three samples: two unique and one longitudinal.
- Presently three different assay platforms by two companies (Innogenetics and MesoScaleDiscovery).
- Coordinated from Neurochemistry Laboratory in Mölndal, Sweden and is sponsored by The Alzheimer’s Association.
- Two publications:
  Mattsson, N. et al, Alzheimer’s & Dementia 2011;7:386-395
Results (QC-L)
Past, present, and future

- 2009: QC program
- 2010: Improvements of existing assays (Industry)
- 2011: New assays (Industry)
- 2012: GBSC (Alzheimer's Association)
- 2013: BIOMARKAPD
- 2014: Improvements of existing assays (Industry)
The big picture

QC-program

- New assays
- Assay improvements
- Certified reference material/method
- Standard operating procedures

High variability
Funding

- The first four years have been funded by a generous grant from an anonymous donor to the Alzheimer’s Association.

- Future funding is not yet clear.
CSF biomarker variability in the Alzheimer’s Association quality control program

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

Background
The cerebrospinal fluid (CSF) biomarkers amyloid-β 1-42 (Ab42), total-tau (T-tau), and phosphorylated-tau (P-tau) are increasingly used for Alzheimer’s disease (AD) research and patient management. However, in addition to significant differences between platform-specific commercial assay kit results, there are large variations in biomarker measurements between and within laboratories. One goal with the Alzheimer’s Association quality control program has been to identify the sources for the variability and thereby improve the reproducibility in the measured values.

Method
Data from the first nine rounds of the Alzheimer’s Association QC program was used. In each round, three pools of CSF samples (one longitudinal and two unique) were analyzed by participating laboratories for tau and Aβ proteins by single analyte enzyme-linked immunosorbent assays (ELISA), a multiplexing xMAP assay (both from Innogenetics) or an immunoassay with electrochemiluminescence detection (Meso Scale Discovery; MSD).

Results
Figure 1 shows the results for the longitudinal sample and the large variations in determining the analytes concentrations are apparent. Coefficients of variation (CV) between the laboratories were around 20-30%, while the between lot CV ranged from approximately 0-20% (Figure 2). Longitudinal within-laboratory CV was 5-19%. Interestingly, longitudinal within-laboratory CVs differed considerably between biomarkers at different laboratories, suggesting that a component of the variability was assay-dependent.

Conclusions
Despite attempts to reduce the overall variability of CSF AD biomarker measurements it remains too high to allow assignment of universal cutoff values for a specific intended use, even for laboratories using the same commercially available assay. Thus, each laboratory must ensure longitudinal stability (lot consistency) in their measurements and use internally qualified cutoff levels.

Take home message
The high between-lab variabilities for the AD biomarkers remain a problem. However, the future carry hope that the imprecisions will be reduced due to improvements of present, and introduction of new assays.

Acknowledgement
A generous grant from an anonymous donor to the Alzheimer’s Association supported this study.

Reference

Date: Sunday, July 14, 2013
Poster Number: P1-178

Figure1. Results of the longitudinal QC sample for the first nine rounds of the Alzheimer Association QC program. At round seven a new sample was introduced and the switch is highlighted by a change in both symbol and background colors. The number of participating laboratories was 84.

Figure2. Relative contribution of between lot and between laboratory to the total variability for INNOTEST and AlzBio3.