Global Biomarkers Standardization Consortium of CSF biomarkers

AAIC Face-to-Face Meeting

July 15, 2017

London, UK

Meeting Summary

Welcome and Introduction

- Jim Hendrix gave the welcome and extended accolades to the Consortium for being the driving force in CSF research and for this year's, best-attended, Biofluids Workshop.

Update on QC Program - Kaj Blennow

- Initiated Alzheimer's Association CSF program with Alzheimer's Association funding, the program was started due to the large variability of absolute levels of CSF Aβ42 across labs displaying the need for standardization efforts.
- Variability is due to pre-analytical factors, analytical factors, and assay manufacturing.
- Started in 2009, 3 rounds per year, 3 QC samples (pooled CSF; 2 unique, 1 same).
- Goals for QC program are for individual labs to monitorST.Vd2an fundiu0 T6.61 CSF biomarker measurements; longitudinal drift in CFS levels; assay performance and batch variation.
- 24 rounds completed to date. 126 total number of labs, numerous assay formats: Innotest ELISA, Luminex, MesoScale bead-based assay, Euroimmun ELISA, Cobas Elecsys, IBL (too few participants for evaluation), Lumipulse from Fujirebio.
- Testing of CSF Aβ(1-42) on Cobas Elecys
    - Minimal batch to batch variability; method aligned to reference measurement procedure of mass spectrometry.
    - Same round comparisons of in between-lab variability: Innotest-17% CV and Cobas Elecys-2.5% CV. -

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	CSF Aβ42 Mean CV (%)	CSF Aβ40 Mean CV (%)	CSF T-tau Mean CV (%)	CSF P-tau Mean CV (%)
Innotest ELISA	15	27	15	12
Euroimmun ELISA	13	16	11	

assays between lab CVs and longitudinal changes.

- When the CSF reference material is available will Kaj be involved

- MS based method, endogenous Aβ40 and an

- 3rd largest PIA, ~600+members
- 4 projects have come forward based on the PIA Day meeting: harmonization and standardization of preanalytics factors in saliva; looking at analytics, how are the bioinformatics methods being used, what is appropriate; context of use and what are the context of use of greatest need; looking at biomarkers from an epidemiological standpoint.
- Sid notified the group that if a

detection.

- Release of AD markers on fully automated platforms:
    - Euroimmune - Aβ42- Q4 2017, Aβ40- Q4 2017, T-tau and P-tau-expected soon
    - Roche - Aβ42- Released, Aβ40-prototype, T-tau and P-tau-expected soon
    - Fujirebio - Aβ42- Released, Aβ40-prototype, T-tau-will be released tomorrow, July 16, 2017, and P-tau-prototype
- Discussion was if the future direction is that samples will be sent to a central lab for testing.

Cut-points for AD biomarkers: Methods & Challenges - Jonathan Schott

- A binary test is preferred; you do or do not have the disease.
- In research an increasing move to use biomarker designations-A/N scheme, A/T/N scheme. There is a need for a cut-point.
- A publication displayed different cut-points for different European centers, a patient would be diagnosed with Alzheimer's differently in different countries due to the variable cut-points
- Few tests are binary, exception genetics, but even in genetics there is a gray zone
- Methods for determining cut-points depend on, or change, sensitivity/specificity balance:
    - Can establish normal reference limits based just on controls. Can maximize accuracy, depends on disease prevalence. Receiver operator curve methods-Youden's index, mixture modeling-all easy when 2 separate Gaussian curves, difficult when overlap.
- For a control group to actually be a control, need another biomarker because 20-30% of elderly individuals may have prodromal AD.
- If you use younger controls, assume that your measures do not change "normally" with age.
- Who is the patient group? Pure AD is rare many have more than one pathology. In clinical practice the issue is not distinguishing AD dementia from controls, but AD from other forms of dementia.
- Beach et al 2012 - postmortem samples, 107/271 diagnosed with non-AD had AD.
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- Henrik Zetterberg stated that one approach is to work with likelihood ratios but need to standardize assays.
- Different pre-analytics cause a problem, different cut offs in different populations
- Jonathan suggested for the group to work towards a central online resource that allows the user to input a value and receive a probability of a diagnosis; the probability would be weighted more when more post-mortem samples are included. This would become more accurate based on the more data inputted.
- Bob-need to be very clear on the question trying to answer. Ex. prognostic questions, do I have someone with a chemical finding that will predict a neuroimaging finding, or pathology finding? Will probably have to lower the expectations on biomarkers, need to use multiple data.
- Jim Hendrix inquired if there is a need for a similar descriptive label for CSF like Amyvid? Jonathan thinks this is a good starting point.
- In Europe, very country specific, CSF sampling tests are used in clinical practice. Clinical utility in Scandinavia, Germany, France, is already there, not stand alone, adjunct measures.
- How to use 3 and 4 biomarkers together? Need to integrate data with clinical and imaging formation.
- In Germany, biomarkers integrated in clinical routine for at least 15 years, performance of biomarkers is fully reimbursed by insurance. Gray zones have been integrated in to their interpretation algorithms for at least 10 years. ~30% of patients diagnosed with AD had LP.
- Which technique should be used to estimate cut-point? Les and several European research groups used as many methods and narrow in on a reasonable cut-point. Statistics will give you a sliding scale between sensitivity/specificity. Decision is do you want to minimize false negatives or false positives or go for accuracy, not a problem as long as it is acknowledged.
- Might need a staged approach for sensitivity and specificity.
- How to get LP more popular in USA? In France, you have to demonstrate that is saves money. In Britain, need champion physicians to demonstrate ease of use, in UK there is a training program for nurses, and need facilities for practicality.
- Maria Carillo stated that for the US government-based reimbursement agency, it is illegal to talk about money, only benefit to the patient. The burden is to demonstrate the diagnosis improves the health outcome. She recommended for the group to attend the IDEAS Study presentation by Gil Rabinovici, which will provide preliminary results of amyloid PET, proving that amyloid imaging can provide a benefit to a health care management of a patient after diagnosis. Need a FDA approved assay; AUC that can be given to the reimbursement agency; and education beyond that.

Concluding Remarks

- Next webinar teleconference will be scheduled in the fall.