Global Biomarkers Standardization Consortium of CSF biomarkers

Tuesday, March 27, 2018

9 a.m. Central/ 10 a.m. Eastern/ 3 p.m. BST

Meeting Summary

CSF Appropriate Use Criteria – Les Shaw

- A workgroup (WG) consisting of experts in the field, was convened February 2017 by the Alzheimer's Association to develop appropriate use criteria with the purpose to assist healthcare practitioners with guidance based on evidence and the experience of WG members, and ethical standards for patient care-on the appropriate and inappropriate use of LP and CSF AD biomarker testing.
- The WG builds on the published 2013 Johnson et al. Amyloid PET AUC and intended to support clinicians in identifying appropriate patients for LP and CSF testing, while also taking in to account the cost-effective use of limited healthcare resources. The goal is to have the AUC an important resource for policy makers & 3rd party payers.
- The AUC did not provide recommendations for the research use of CSF biomarker testing or rule out conditions other than AD or MCI-AD as possible causes of cognitive decline.
- The CSF AUC focuses on CSF Aβ42 (sometimes normalized to Aβ40), t-tau and p-tau181 (and ratios to Aβ2 in some studies).
- WG holds regular meetings and works with Avalere Health, a healthcare consulting firm that provides technical and editorial assistance. WG members were chosen due to considerable publications on topics relevant to the use of LP.
- The WG defined the scope and parameters of the AUC and key research questions to guide a systemic review of published data on LP & CSF using PICOTS (**p**opulation, **i**nterventions-who is the patient, what are the interventions in testing, **c**omparisons-against reference standard; clinical diagnosis, amyloid PET or autopsy diagnosis of the testing interventions, **o**utcomes, **t**iming and settings-in which the studies were done) framework.
- The WG developed 5 key questions surrounding LP and each one was reviewed based on known literature.
- KQ1-Safety of LP
  - CSF can be collected safely and reliably by LP, to maximize safety is to recognize patient and LP related risk factors; keys to safety and effectiveness to decrease fear of the procedure is for the clinical staff to have verbal communication about the procedure.
- KQ2- What is the diagnostic accuracy In persons experiencing cog impairment of CSF Ab42 & tau (t-tau, p-tau) or ratios of analytes as indicators of AD pathology presence or absence?

        - Diagnostic accuracy based on clinical criteria alone is not optimal, sensitive and specificity is ~80% & 70%, respectively, and at earlier disease stages accuracy is substantially lower.
        - From the systemic review the majority of the studies the reference standard was clinical diagnosis but the WG supplemented it by using amyloid PET detection of AD pathology as the reference standard.
        - Using amyloid PET as the reference standard increases sensitivity and specificity.
    - The WG rated 14 clinical indications as either appropriate or inappropriate.
    - Currently, expert reviewers are reviewing the manuscript and their feedback will be incorporated before the submission of the publication.

CSF Pre-analytics Protocol – Jim Hendrix

- The Alzheimer's Association convened a WG comprised of various companies and academic participants to develop a consensus around a CSF pre-analytical protocol.
- The consortium plans to present an oral presentation at AAIC and at the F2F GBSC meeting. Jim will provide an update at AAN.
- The objective of the pre-analytical protocol is for it to be utilized in clinical practice and simple to use.

Working in Parallel with the CRM Release – Ingrid Zegers & Henrik Zetterberg

- 3 Aβ42 certified reference materials were released in December 2017.
- The 3 CRMs are of different levels and assigned using mass spectrometry reference methods measured in 5 different labs. Values are:
    - Certified value 0.45 µg/L with an uncertainty $U_{crm,rel}$ of 0.07 µg/L
    - Certified value 0.72 µg/L with an uncertainty of 0.11 µg/L
    - Certified value 1.22 µg/L with an uncertainty of 0.18 µg/L
- The expandable uncertainty, which is on the certificate, is a conservative assessment of a 95% confidence interval, if have to reproduce the whole process, with new material, fresh with new measurements, expect to have the value of the new material consistent with the certified value of the present one within the uncertainty interval.
- Uncertainty due to the characterization by reference method is the largest value because the largest variations were between lab variation and between-day variations.
- Focus now is how to use the CRMs to standardize routine samples.
- Metrological traceability-In Europe, their regulations requires that manufacturer's kit calibrators should have values that are traceable to higher order reference materials if available.
- Traceability is based on calibration.
- Calibration is quantity value of the CRM->signal (indication) -> Measurement result.
- Aβ42- dilutional linearity not a given, handling issues, in-house and kit calibrator may not be commutable, because of these issues it was decided to produce 3 different levels; the 3 levels could be mixed to produce intermediate calibrators.
- First test with Innotest ELISA had the data from the CRM and calculated concentrations of the mixtures align for dilutional linearity of experimental and theoretical values. Works if mixture is produced directly in ELISA plates
- If mixed in Eppendorf tubes there is a huge loss of Aβ42 with absorption of Aβ

to tubes and a lower value for the intermediate point.
    - Sarstedt Low binding screw cap micro tube was advised for use.
    - Euroimmun studies for implementation of CRM outlook: method development for proportional dilution will require further optimization: # of intermediary points, robustness, extrapolation to low and high. Generations of secondary standards, sample selection, homogeneity .value assignment.
    - Commutability study III data can be used to assess to which extent it would be possible to harmonize the different methods using the CRM. Can use the slope from the CRM data to calculate the correction factor and apply it to the clinical samples, this result in harmonization of the clinical samples.
    - Aβ42 assays are performing very well and should be able to achieve harmonization.
    - Conclusions: Different approaches for calibrations; If mixtures prepared: handling should be optimized; a protocol should be developed; very good alignment between methods is possible; need to prepare pools for verification/validation or if the QA program is sufficient for that?
    - Ingrid is having a meeting with manufacturers in May and plans to prepare a publication.

- Quincke vs. Sprotte needles. Still clinician personal preference, useful if there was study data from best practitioner with each needle type but CSF AUC WG recommend an atraumatic needle based on the available literature.
- Is there a recommendation of an optimal method for transfer of Aβ value? Results look very good, different approaches can be used but need to be validated using their quality control materials and re-measuring CRM. Different in companies based on the nature of in house calibrators and kit calibrators.
- The Alzheimer's Association can explore the option, as an extension of the QC program, to sponsor and provide CSF pools that can be used by vendors to transfer the assays and make the link to the CRM.

F2F Meeting

- AAIC Chicago in-person meeting – Saturday, July 21, 6 -9 p.m., Marriott Marquis Hotel, Burnham Room