

Global Biomarker Standardization Consortium and Standardization of Alzheimer's Blood Biomarkers
Tuesday, October 30, 2018
10 a.m. – 12 p.m. ET
Meeting Summary

Welcome

- Rebecca Edelmayer, Director, Scientific Engagement, Alzheimer's Association, has replaced Jim Hendrix as the facilitator of the GBSC.

Global Biomarkers Standardization Consortium

- Certified Reference Material Manufacturers' Pilot Study Publication - **Britta Brix**
 - Data that was previously presented at the GBSC AAIC 2018 in-person meeting will be merged with Ingrid Segers manuscript with the plan to publish soon.
 - The companies are in discussion regarding the possibility of conducting a second study using samples provided by Kaj Blennow. Britta Brix will disseminate a draft protocol to send to the other companies.
 - Les Shaw is involved with certified reference materials (CRMs) in mass spectrometry methods, he is willing to collaborate with Britta and share data.
- Tau Reference Methods & Materials – **Henrik Zetterberg**
 - Selected a stable reporter fragment. Endogeneous tau in 340 µl CSF-Digested, CSF results displayed that digested tau was being measured, not a contaminant or endogenous peptide.
 - Native tau in CSF- t-tau ~650 pg/ml, CV-4.6%.
 - Innotest ELISA-measured 3 concentrations of t-tau, MS signals corresponded with concentration levels.
 - Next steps
 1. 1st Round Robin study with 1-20 CSF samples. If any labs are interested to participate send an email to johan.gobom@neuro.gu.se.
 2. Round Robin study II (MS-based tau methods with the same calibrator)
 3. Commutability study with candidate reference materials, patient CSF samples and MS and immunoassay-based assays
 - The plan is to begin the Round Robin January 2019

Standardization of Alzheimer's Blood Biomarkers

- Review of table/information compiled by the Biofluid Based Biomarker PIA on plasma amyloid-β literature/data – **Silvia Fossati and Michelle Mielke**

- The Biofluid Based Biomarker PIA has 3 Work groups: Saliva, Context of Use, and Reference Ranges.
- The Reference Ranges WG performed a literature search and compiled a list of the pre- and analytical variables to understand the confounding factors and their study variability.
- Reference Ranges WG has 22 members and Michelle Mielke is the Chair. Goals are:
 1. Identify and decide on a few promising biofluids based markers that can be used at the general physician level
 2. Compare/contrast study sample collection, assays, populations
 3. Establish 'normal ranges'
 4. Decide on how best to move forward
 5. Identify studies interested in donating samples
- Created a checklist comprised of sample collection, assay information (analytical and clinical) tested checklist on 4 recent papers on amyloid beta and shared with the group.
- Pre-analytical variables- 13 variables based on literature and experts of the group, i.e. time of collection, fasting status, tube types, needle size and location of draw, freeze-thaw cycles, etc. In the 4 papers they reviewed there wasn't much description of pre-analytical variables.
- Assay methodology and biochemical process variables
 - Ex. quantitative, calibration standards used, assay sensitivity, assay specificity, etc.
- For the Assays (including clinical performance) and statistical analysis variable the WG looked at intended context of use, dependent variable, independent variable.
- Study population: sample size, age, sex, diet, gestation, medications, no-AD comorbidities.
- Insights from this exercise are: comprehensive pre-analytical variables are lacking in original research studies; the purpose of those original research studies were not designed to study pre-analytical/analytical variables; study of these variables require a specific design. Also learned, study results are due to many factors such as patient population. Can perform a Round Robin to measure assay method and performance difference.
- Should the standardized protocol be applicable to all promising AD blood biomarkers? The most promising biomarkers are NfL, p-tau, t-tau, then amyloid beta.
- Questions posed by the WG:
 1. Should the standardized protocols be analyte and/or method specific?
 2. If so, what blood analytes and methods should these standardized protocols include?
 3. Can we establish best pre-analytical protocols form the literature or do we need to test them in new studies?
 - Henrik Zetterberg suggested to design a study for a gold standard from sample collection and processing, identify the results when testing the irrelevant variables, and establish a protocol that can work in a general practitioner's office.
 - Can also compare running the same sample on different days.

- Sid O' Bryant commented that standardization might be unlikely. Some of the protocols used from the research wont translate to clinical. Ex. Quest Diagnostics parameters around markers can vary.
 - Henrik suggested to design a study where they mimic Quest Diagnostic procedures and compare that to what the group determines is the gold standard.
 - Sid will ask Quest Diagnostics for their protocol and Michelle will work with Sid. Henrik will send the publication in DaDM on comparison of transport to the GBSC and SABB. Charlotte Teunnison volunteered to participate and will do in parallel the same for amyloid.
 - This will be a comparison of an ultimate protocol vs. real world protocol.

- Preview of Vision for Round Robin Testing of Blood Samples as part of QC Program Expansion – **Kaj Blennow**
 - Primary aim is to examine how the assays compare, how tightly they correlate to measure Aβ42 and Aβ40.
 - 70 individual plasma samples comparing ~ 10 different methods.
 - Plan to have the results by March and would like to present at AAIC 2019.
 - Would like to expand the QC for blood, they will take on labs that are focused on blood but it is has to be assays that are generally available. They will need 3-4 labs that are using the same assay for participation.
 - This can be discussed at upcoming Alzheimer's Disease Centers meetings. They have a standardized blood repository which includes plasma, cells, and serum which can support QC studies.
 - It was suggested to add Robert Rissman to this project.

- Roche - Recommendations for blood sample collection and plasma storage for analysis of blood-based biomarkers for AD in RESEARCH STUDIES - **Malgorzata Rozga**
 - Perimeters evaluated: circadian rhythm, anticoagulant, tube parameters, whole blood stability in EDTA tube, number of tube transfers, effect of a collection tube during freezing, freeze thaw cycles.
 - Recommendations are: EDTA tube filled to max volume, centrifuge between 30-60 minutes, freeze immediately to -80°C or fresh plasma storage at 4°C, up to 5 tube transfers, shipment via dry ice, thawed plasma storage at 4°C before measurement or fresh sample storage 4°C before measurement, both no longer than 2 hours.
 - The data will be published in the next couple of weeks, Malgorzata will send the CTAD presentation to the group.
 - The measurements where conducted on the Elecsys platform.

- SABB November 29, 2018 Face-to-Face Agenda
 - The meeting will be held in Washington D.C. 6-8:30 p.m. there will be a teleconference line provided for remote attendees.

- Goals of the meeting are to: 1.) Gather hard data and the literature available; 2.) Defining analytes and platforms of interest 3.) Fill in the gaps 4.) Discuss experiments and draft protocols. Members should work on this beforehand.
- Richard Margolin suggested to interact with imaging and neuropathology communities and get cross fertilization. As these mature what is the correlation between blood based findings with imaging and neuroimaging.
- Create more visibility in imaging community, potentially a presentation of this work at the AAIC Neuroimaging Preconference.
- Outreach with the Biofluid Based Biomarkers and Neuroimaging PIAs. April will connect Rich Margolin with Michelle Mielke.
- Also can incorporate with Alzheimer's Disease Centers Meetings-Doug Galasko will follow up on this.
- Robert Rissman is involved in a primary care study with imaging and MRI.