Standardization of Alzheimer's Blood Biomarkers: Pre-analytical Protocol Workgroup

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Global Biomarkers Standardization Consortium (GBSC)

Gathers key researchers, clinicians, and industry, regulatory and government leaders in Alzheimer's disease to achieve consensus on the best ways to standardize and validate biomarker tests for use in clinical practices around the world.

The Case for CSF Analysis

- Traditionally clinicians have diagnosed AD using primarily clinical criteria

- CSF AD biomarkers are effective surrogates for neuropathology

- Their use provides for reliable detection of AD earlier in the disease course compared to clinical diagnosis alone

- Reliability of CSF AD biomarker testing for amyloid and tau proteins has advanced considerably within- and across platforms, increasing the likelihood of broad clinical use internationally including in USA where this is typically done in the research realm

- CSF biomarker testing has IVD status in some European countries:

  - in routine clinical practice

  - for patient selection in international treatment trials

GBSC Working Groups for CSF

Reference Materials

- Certified Reference Material (CRM) for Ab_{1-42} released from the IFCC (2017) for calibration of instruments
- The CRM will be used to recalibrate instruments world-wide

IFCC =International Federation of Clinical Chemistry and Laboratory Medicine

Reference Methods

- Quality Control project established standardized methods between labs
- Two standard methods approved by JCTLM for $A\beta_{1-42}$ measurement Blennow (2015) & Shaw (2016)
- Additional methods being developed

JCTLM =Joint Committee for Traceability in Laboratory Medicine

GBSC Working Groups for CSF

Appropriate Use Criteria

- Work group of international AD and CSF experts convened by the Alzheimer's Association

ELSEVIER

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Alzheimer's & Dementia

Review Article

Appropriate use criteria for lumbar puncture and cerebrospinal fluid testing in the diagnosis of Alzheimer's disease

Leslie M. Shaw[a], Jalayne Arias[b], Kaj Blennow[c], Douglas Galasko[d], Jose Luis Molinuevo[e], Stephen Salloway[f], Suzanne Schindler[g], Maria C. Carrillo[h], James A. Hendrix[h,*], April Ross[h], Judit Illes[i], Courtney Ramus[i], Sheila Fifer[j]

Pre-analytical Consensus Protocol

- A working group of international companies and academics convened by the Alzheimer's Association

Manuscript in Development

LP CSF Appropriate Use Criteria

- Assist healthcare practitioners with guidance-based on: **evidence** and the **experience** of the workgroup members, and **ethical standards** for patient care-on the ***Appropriate*** and ***Inappropriate*** use of LP and CSF AD biomarker testing to support optimal patient safety & care.

- Builds on the AUC for amyloid PET (*Johnson, 2013*), these criteria are intended to support clinicians in consistently identifying appropriate patients for LP and CSF testing, while considering the cost-effective use of limited healthcare resources.

- It is hoped that these AUC will be an important resource for policy makers & 3rd party payers

These AUC *do not:*

- Provide recommendations for the research use of CSF biomarker testing
- Rule out conditions other than AD or MCI-AD as possible causes of cog decline

Recommendations for the appropriate use of CSF are made in the context of the many other diagnostic tools in use

Standardization of Alzheimer's Blood Biomarkers (SABB)

- Blood as a potential biomarker
- A working group of international researchers and diagnostic companies
- Focus: Gain consensus on pre-analytical blood biomarker SOP
- Not analyte or platform specific
- Leaning mostly towards plasma vs. serum
- Discussing universal method with global feasibility
- For research purposes but considerations are being made for real-world implementation

Call for Pre-Analytical Protocols

- Florey (AIBL)
- Mayo Clinic
- Univ. of Minnesota
- Penn (ADNI)
- Penn (Penn Neurology)
- UCSD (ATRI/ADCS)
- Univ. of Gothenburg
- Temple University
- VU Univ. Med Center
- Washington Univ. St. Louis
- NCGG

- ADx NeuroSciences
- Araclon
- Biogen
- C2N Diagnostics
- Cytox
- DiamiR
- EUROIMMUN
- Janssen
- MagQu
- MSD
- NanoSomiX

- PeopleBio
- Predemtec
- Quanterix
- Roche
- Saladex
- Shimadzu
- Vivid Genomics

- NCRAD
- NIH/NIA

Pre-analytical Variables / Factors
19 Under Discussion

Sampling

- Time of day for collection
- Fasting status
- Needle size and Location of draw
- Vacutainer needle vs. Butterfly needle vs. Syringe
- Plastic tubing or other 'tools' used during draw
- Anticoagulant type and Concentration
- Tube types and additives, e.g., EDTA, acid citrate, heparin
- Tube collection order
- Tube filling volume

Pre-analytical Variables / Factors
19 Under Discussion

Preparation

- Tube inversion or manipulation before centrifugation
- Time from collection to centrifugation
- Temperature during period from collection to centrifugation
- Centrifugation parameters (specify speed, time, temp)
- Time from centrifugation to freeze
- Temperature during period from centrifugation to freezer

Pre-analytical Variables / Factors 19 Under Discussion

Storage

- Temperature of freeze
- Freeze-thaw cycles
- Aliquot size
- Length of storage stability at low temperature (specify 4℃, -20℃, -80℃)

What has actually been tested?

- Even though many labs were using SOP, few labs had actually tested pre-analytical factors

- Agreement that testing all 19 factors to determine consensus would be complex

Analysis of Pre-analytical Protocols

Survey of SABB Members

- *Based on the findings, we conclude that it is too early to define a unified consensus SOP for now.*

- *We do not have sufficient knowledge on the effects of pre-analytics on brain-derived blood biomarkers.*

Variables

RED: Regarded as most relevant to study by SABB

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Next Steps

- Re-convening to rank importance of variables
- Build study proposal to assess variables
- Analytes under discussion include Aβ, Tau, NFL
- MS, IA, and even nucleic acid platforms are still under consideration
- Assessing interest in active partners for testing

For More Information…

More about Alzheimer's Association GBSC initiatives:

https://www.alz.org/research/for_researchers/partnerships/biomarker_consortium/gbsc_working_groups

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