FLUID BIOMARKERS OF CEREBROVASCULAR DISEASE

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THE UTILITY OF FLUID BIOMARKERS

- Fluid biomarkers are easily obtained at a low cost and without the need of a site having specific equipment.

- A single fluid sample gives sufficient volume for the assessment of multiple analytes.

- Fluids can be shipped between institutions, or from rural health care facilities to centers for analysis and interpretation.
THE CHALLENGES OF FLUID BIOMARKERS

- As opposed to direct imaging of vessels / brain tissue in MRI, fluid biomarkers will be surrogates of pathologic processes.

- Sample preparation, storage methods, tube type, time of day, fasting state, unrelated illnesses, and medications, can all affect assay results.
MARKVCID - A UNIQUE OPPORTUNITY FOR US TO EVALUATE BIOMARKERS IN A RIGOROUS, REPRODUCIBLE MANNER

- There is **NO** wholly validated biomarker for cerebral small vessel disease.

- There are many single-site, single-cohort studies that report a novel biomarker. These have yet to be validated and reported as proven.

- This consortium aims to produce a battery of biomarkers that are validated across sites, across cohorts, and across platforms, that are useful for diagnosis, clinical trials, and tracking of disease.

- Sites are focusing on neuroimaging and fluid biomarkers.
OVERCOMING THE CHALLENGES

- Highlights of this document include requirements for:
  - Fasting, morning sample collection.
  - Standard needle size and type.
  - Standard tube types for collection and storage.
  - Standard aliquot size.
  - Standard temperature requirements for storage.
- Implement best practices that all sites will be required to follow for the collection and storage of samples.
- Document and detail deviations from the best practices to allow inclusion in statistical analyses.
**EXPECTATIONS OF MARKVCID SITES.**

- Sites collecting fluid biospecimens will comply with best practices, beginning as early as possible but by the start of the UH3 phase.

- Sites will maintain samples at the required temperatures, de-identified using the MarkVCID coding system.

- Sites will aliquot and store a minimum volume of 5ml plasma and CSF that will be designated specifically to MarkVCID.

- Requests for samples will be reviewed and approved by the fluid biomarker subcommittee, for final approval by the steering committee.

- The sample shipping SOP will be followed when samples are to be shipped out.
IMPROVING SHARING

- A specific sharing subcommittee worked extensively on language of MTAs and consent forms.

- IRBs were updated to include common language.

- Now, these sharing forms are in place so that prospective collection of samples in UH3 will allow full sharing of samples between all of the consortium sites.

- Decision was made to maintain samples as a “virtual biorepository” but with centralized sample inventories.
MARKVCID MODEL FOR CROSS-SITE VALIDATION

- Site 1 proposed biomarker(s)
- Sites 2, 3 and 4 run their samples
- Sites 5, 6 and 7 provide samples
- Data collated at Coordinating center
CROSS-SITE VALIDATION KIT 1: ENDOTHELIAL SIGNALING KIT - PLASMA

- Composite biomarker of three plasma proteins: VEGF-D, PIGF, and bFGF.
- Measurements using Meso Scale Discovery V-Plex platform.
- Rationale is that endothelial dysfunction early in cerebrovascular disease causes compensatory upregulation of endothelial & angiogenesis signaling.
- Longitudinal preliminary data showed that baseline signal predicts accelerated white matter injury and cognitive decline measured by a composite memory score.
- Cross-sectional data demonstrate association of Endothelial signaling with higher cerebral free water and lower whole-brain FA, even after controlling for presence of amyloid on PET.
CROSS-SITE VALIDATION KIT 2: ENDOTHELIAL INFLAMMATION KIT – PLASMA EXOSOMES

- Composite biomarker based on quantifying immune activation by measuring CBb, C3b, and C1q in endothelial-derived exosomes.

- Based on model that posits endothelial inflammation at an early stage of cerebrovascular disease.

- Preliminary data show marked separation between normal subjects with and without white matter hyperintensities.

- Based on model that posits endothelial dysfunction at an early stage of cerebrovascular disease.
CSF PLGF – placental growth factor, is significantly associated with WMH volume in a cohort of individuals who are cognitively normal or diagnosed with MCI and have high cardiovascular risk burden.

- **P<0.001 for regression; R² = 0.679.**

CSF PLGF measured using Quanterix Simoa.

CSF PLGF also associates moderately with trail-making tasks and WAIS scores.

CSF PLGF may be a promising biomarker for cerebral small vessel disease.
UNIVERSITY OF KENTUCKY DATA – PLASMA TNF AND MMP1

**Plasma MMP1 - WMH Correlation**

![Graph showing the correlation between Plasma MMP1 and WMH volume. The correlation coefficient is r = -0.28, with P = 0.05.]

**Plasma TNFα - CBF Correlation**

![Graph showing the correlation between Plasma TNFα and CBF. The correlation coefficient is r = -0.92, with P = 0.01.]

Fluids, both plasma and serum, provide an opportunity to identify biomarker profiles for neurodegenerative and cerebrovascular diseases.

Unlike our existing PET capabilities, which provide amyloid and tau information, fluid biomarkers may allow us to identify the presence of multiple pathologies.

The two kits that have advanced to cross-site validation in MarkVCID are focused on endothelial responses, which may also afford unique opportunities to identify novel therapeutic targets.

Fluid biomarkers are likely the optimal method for tracking target engagement and efficacy in clinical trials for VCID.
FUTURE VISION

One-size fits-all medicine

Stratified medicine

Precision medicine

Stratification
Patients are grouped by: Disease Subtypes Demographics Clinical features Biomarkers

Personalisation
Patient individual:
Preferences, Clinical features Medication history Environment Behaviours & habits Biomarker

Precision medicine
THANKS TO ALL

MarkVCID Fluid Biomarker Subcommittee

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