NIH VCID Biomarkers Consortium focused on the large unmet need for clinical trial-ready VCID biomarkers with high potential for positive impact in public health

Phase II: Small Vessel VCID Biomarkers Selected for Independent Multi-Site Testing and Validation

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MarkVCID Takes Aim at Clinical Trial Ready Small Vessel VCID Biomarkers

- Steve Greenberg*, MD, PhD, MGH (Coordinating Center)
- Joel Kramer*, PsyD, University of California, San Francisco, Charles S. DeCarli, MD, University of California, Davis
- Hanzhang Lu*, PhD, Marilyn Albert, PhD, Johns Hopkins
- Gary Rosenberg*, MD, Arvind Caprihan, PhD, University of New Mexico Health Sciences Center
- Julie Schneider*, MD, Rush University, Konstantinos Arfanakis, MD, Illinois Institute of Technology
- Sudha Seshadri*, MD, University of Texas Health, San Antonio, Myriam Fornage, University of Texas, PhD, Russell P. Tracy, University of Vermont
- Danny JJ Wang*, PhD, Amir Kashani, MD, John Ringman, MD, University of Southern California
- Donna Wilcock*, PhD, Gregory Jicha, MD, PhD, University of Kentucky
Biomarkers that measure...

*Small Vessel Disease (e.g.):*
- Atherosclerosis
- Arteriolosclerosis
- Capillary Disease
- Cerebral Amyloid Angiopathy
- Venule Disease

Cognitive Impairment, Including Dementia

...to reflect pathological and clinical impact of small vessel VCID

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**Vascular Injury**
**Immune**
**Metabolic**

**Neurovascular Unit**
**BBB Injury**

**Parenchymal Proteinopathy**
- amyloid, tau, TDP-43, Lewy bodies
MarkVCID is a Staged Team Project

Team approach in which all sites are vested in successful VCID biomarkers.

**UH2 (Y1-Y2) Start = 9/2016**
- Feasibility of specific biomarkers
- Building the consortium
- Standardized, optimized protocols; core clinical data
- Sharing agreements, both internal and external to MarkVCID

**UH2 to UH3 Transition Report = Now**
- Sites propose biomarkers for multi-site independent validation studies

**UH3 (Y3-Y5)** - Multi-site independent validation studies

- **Ideal Outcome**: Validated small vessel VCID biomarkers ready for large scale multi-site clinical research including interventional trials
MarkVCID Biomarker Kits: Selection Process

- 36 biomarker kits proposed, with collaborating sites
- Reviewed by Coordinating Center PI (Greenberg) and External Advisory Committee (Petersen, Montine, Gottesman, Biessels)
- NINDS made decisions that directly reflect review
- Seven selected biomarker kits will submit a detailed finalized multi-site validation protocol for final consideration
  - 5 imaging-based; 2 fluid-based
- All seven were proposed as biomarkers for small vessel VCID risk stratification for entry into clinical trials; some may also be valuable for progression and response to therapy
**MarkVCID Biomarker Kit: MRI Biomarker - Peak Skeletonized Mean Diffusivity**

**Rationale:** PSMD is an index of MD dispersion in the WM MRI “skeleton” that indicates microstructural injury and is a biomarker for small vessel VCID

- **MD** = extent of diffusion of water molecules in that voxel of tissue;
- **Higher MD** = greater WM injury

**Marker of Risk Prediction/Stratification**
(for selection into VCID trial)

Robust measure across MRI machines
- Reliable across DTI acquisition parameters
- Fully automated
- Tested in CADASIL and in population cohorts
- Better marker of progression than Brain Volume, WMHV and lacunes
- Added information to age-, sex, HTN, DM, smoking
- Associated with processing speed, Executive function and memory
**MarkVCID Biomarker Kit:**

**Cerebrovascular Reactivity (CVR)**

- Imaging biomarker
- Evaluate composite vasodilatory capacity of brain’s neurovascular units
- Dynamic acquisition of BOLD MRI images while briefly modulating the participant’s blood CO2 level (inhaling 5% CO2 for 50 seconds)

![Brain images showing normal, MCI, and dementia stages](image)

![Graph showing correlation between MoCA score and whole-brain CVR](graph)

\[ r = 0.46 \]
Bayesian algorithm based on quantitative prior segmentations, Gaussian likelihood and posterior probability constraints

May be used on single FLAIR images or combined with tissue segmentation of high resolution T1 weighted imaging

Executables can be downloaded from: http://idealab.ucdavis.edu/software/index.php
WM MRI signal growth is created from co-registration of baseline and Year 1 FLAIR images, followed by creation of subtractive WMH masks.

- The penumbra in any unique individual is comprised of distinct regions of WMH growth as well as regression.
- Can measure both positive and negative impact of disease progression and effects of interventions on VCID.
- Total penumbra is highly correlated with longitudinal change in WMH, demonstrating minimal distortion in the co-registration procedure.

\[ R^2 = 0.998, \ p < 0.001 \]
**MarkVCID Biomarker Kit:**
MRI Biomarker of Arteriolarosclerosis

**Development** – Ex-vivo MRI linked to pathology (n= 105) to train classifier to identify moderate to severe arteriolarosclerosis, then develop further for in vivo.

**INPUT: MRI MEASURES**
--WMH (8 features)
--diffusion anisotropy (4 features)
--demographics (3 features)
(15 features in total)

**OUTPUT: SCORE**
Higher scores represent arteriolarosclerosis pathology and correlate to cognitive decline/impairment

**Preliminary Validation:**
**Cognition:** Score associated with lower language (p=0.025) and marginally lower visuospatial ability (p=0.05), controlling for age, sex and education.

**In Vivo MRI:** Translated in 24 MAP/ROS participants with in-vivo MRI who died: Obtained an AUC=0.83 for prediction of arteriolarosclerosis based on in-vivo MRI data.
MarkVCID Biomarker Kit:
Endothelial Signaling Kit

- Composite risk stratification biomarker of three plasma proteins: VEGF-D, PlGF, 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
- 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
MarkVCID Biomarker Kit:
Endothelial Inflammatory Kit

- Composite biomarker for disease stratification based on quantifying innate immune activation by measuring (CBb, Bb) within endothelia using 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
Multi-site validation studies
Nomination of revised or new biomarker kits for next set of biomarker kits to undergo multi-site validation
Resource for the VCID scientific community
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