

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

SFN, November 7, 2018

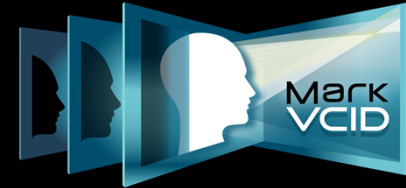


National Institutes of Health

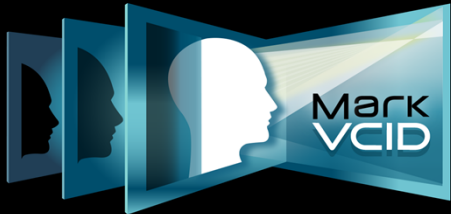
National Institute of Neurological Disorders and Stroke
National Institute on Aging

Roderick A. Corriveau, Ph.D.
Program Director and
Program Lead, ADRD Programs and Summit

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



Biological Framework: Small Vessel VCID Biomarkers

*Biomarkers that
measure...*

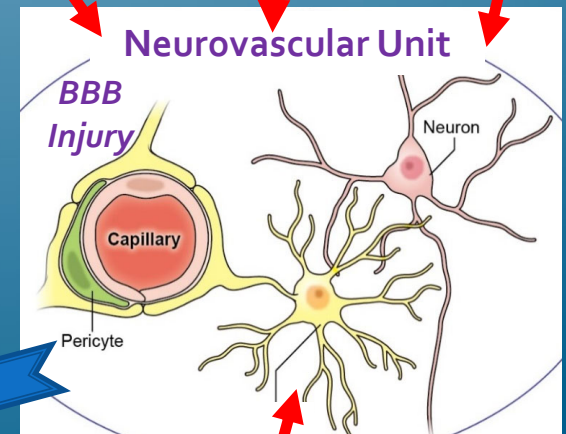
Small Vessel Disease (e.g.):

Atherosclerosis
Arteriolosclerosis
Capillary Disease
Cerebral Amyloid Angiopathy
Venule Disease

Vascular
Injury

Immune

Metabolic



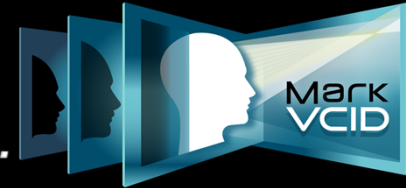
Cognitive Impairment,
Including Dementia

*Parenchymal
Proteinopathy*
amyloid, tau,
TDP-43, Lewy bodies

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

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

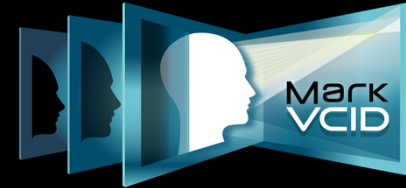
UH2 to UH3 Transition Report = Now

- Sites propose biomarkers for multi-site independent validation studies

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

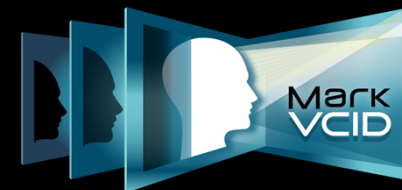
- Ideal Outcome: Validated small vessel VCID biomarkers ready for large scale multi-site clinical research including interventional trials

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

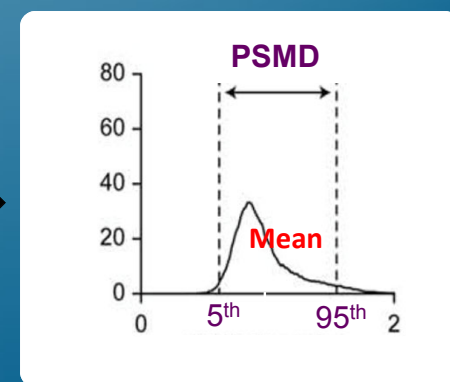
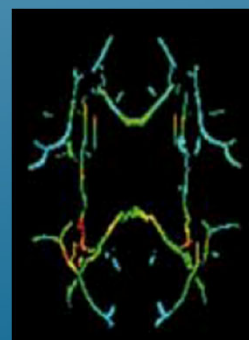
- **MD** = extent of diffusion of water molecules in that voxel of tissue;
- **Higher MD** = greater WM injury

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

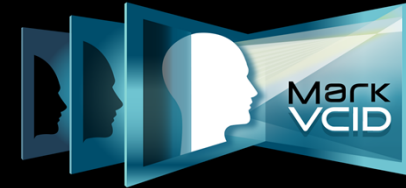
Robust measure across MRI machines

- 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

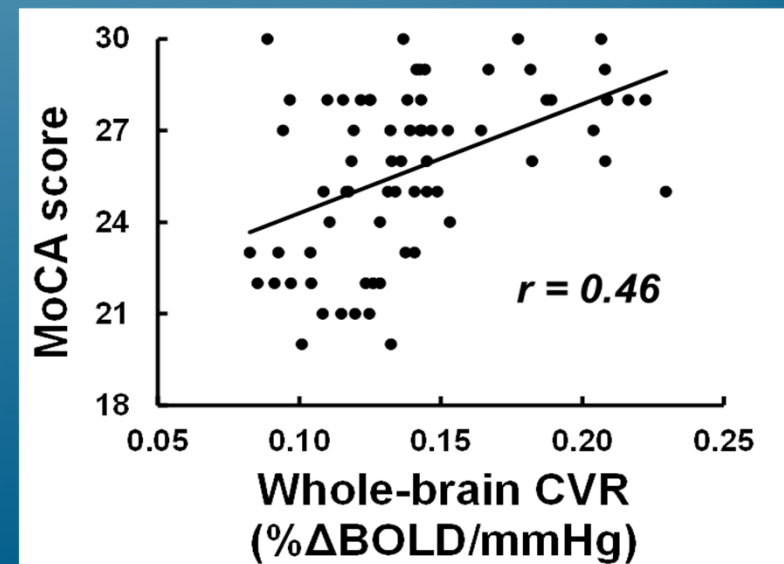
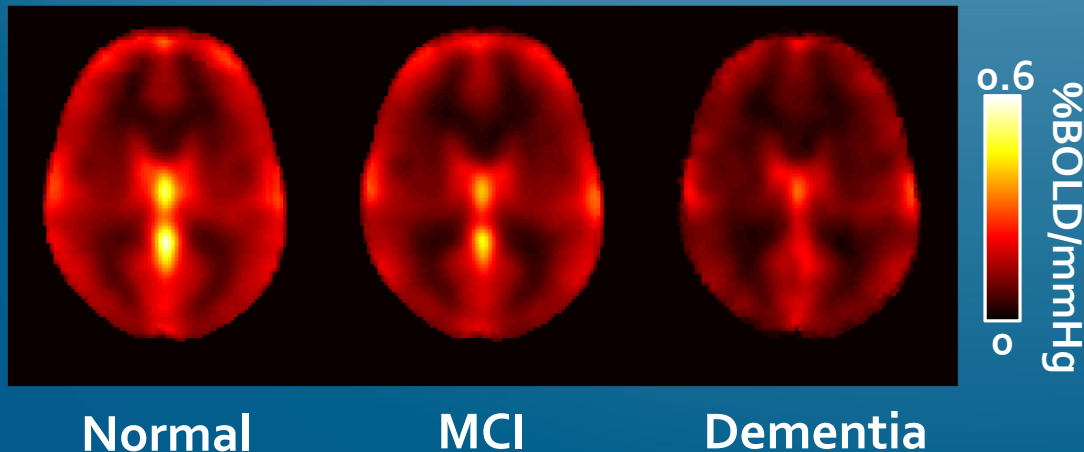
MD on skeleton



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)



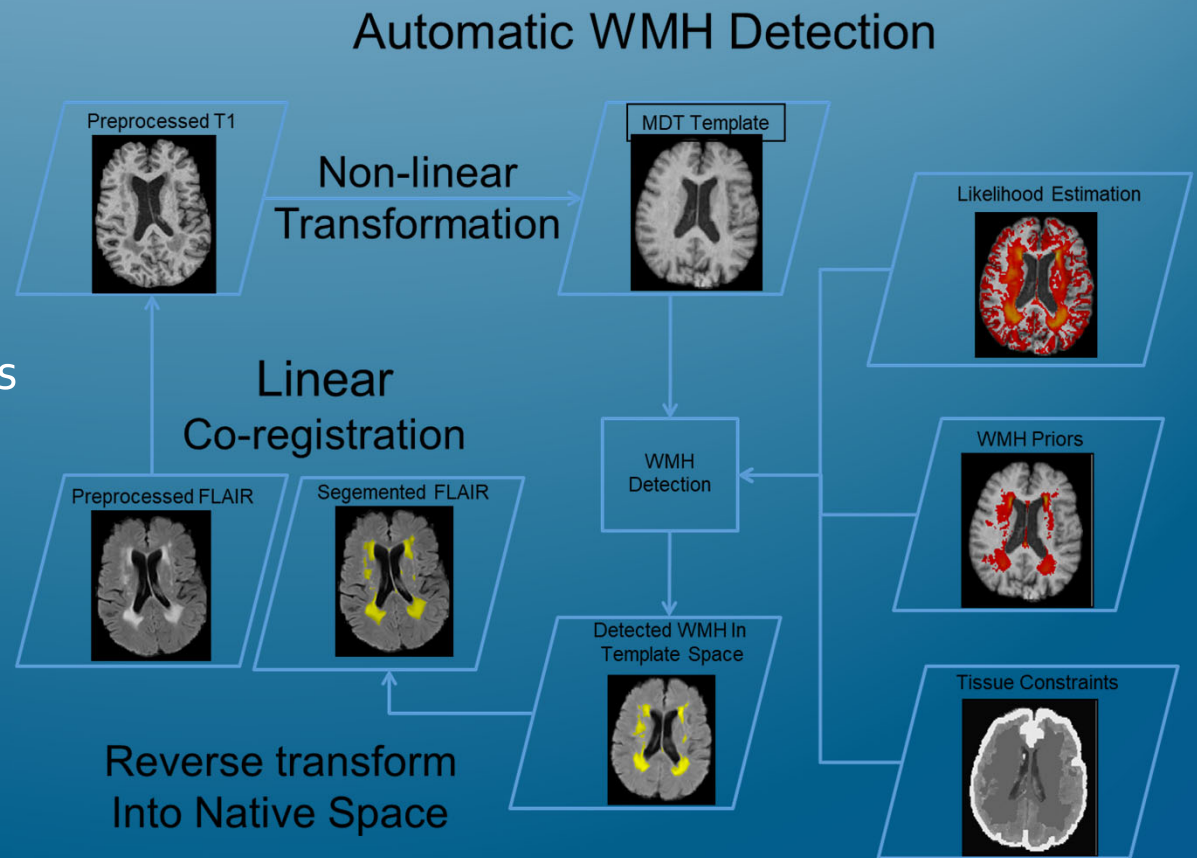
MarkVCID Biomarker Kit:

Cross-Sectional WMH Imaging Biomarker

Bayesian algorithm based on quantitative prior segmentations, Gaussian likelihood and posterior probability constraints

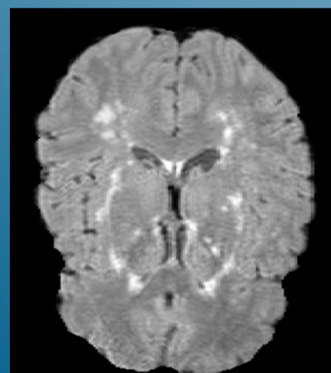
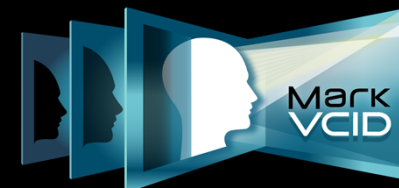
May be used on single FLAIR images or combined with tissue segmentation of high resolution T₁ weighted imaging

Executables can be downloaded from: <http://idealab.ucdavis.edu/software/index.php>



MarkVCID Biomarker Kit:

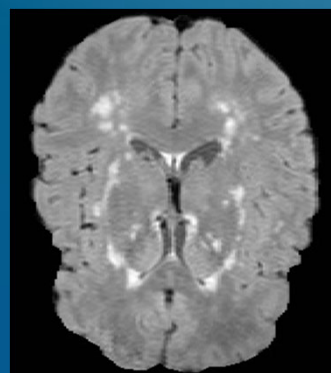
Longitudinal WMH from 3-D FLAIR



Baseline visit FLAIR



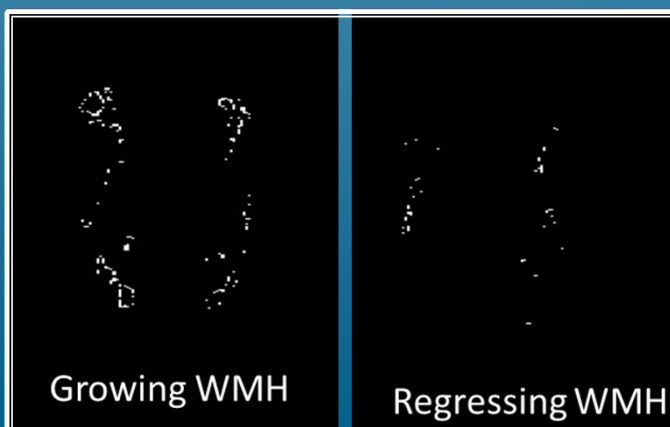
Baseline WMH



1 year visit FLAIR



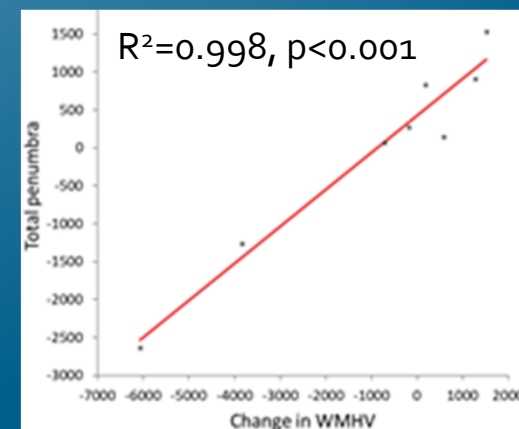
1 year WMH



Growing WMH

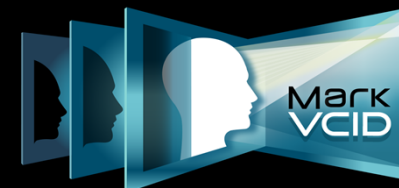
Regressing WMH

- 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



MarkVCID Biomarker Kit:

MRI Biomarker of Arteriolosclerosis



Development – Ex-vivo MRI linked to pathology (n= 105) to train classifier to identify moderate to severe arteriolosclerosis, 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 arteriolosclerosis pathology and correlate to **cognitive decline/impairment**

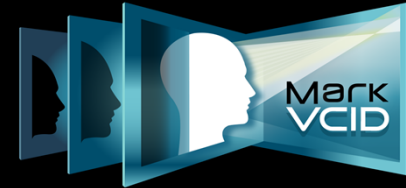
Preliminary Validation:

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 arteriolosclerosis based on in-vivo MRI data.

MarkVCID Biomarker Kit :

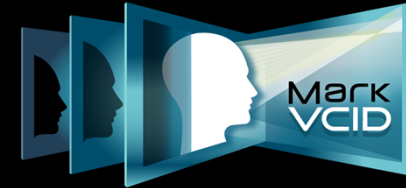
Endothelial Signaling Kit



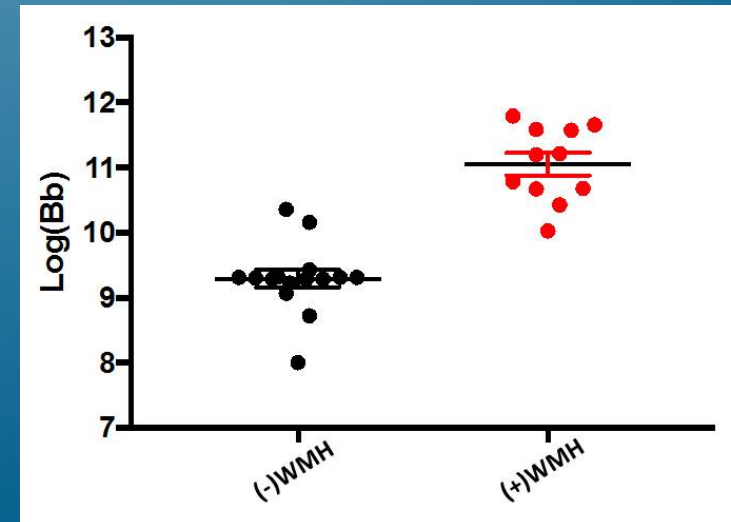
- Composite risk stratification biomarker of three plasma proteins : VEGF-D, PlGF, and bFGF
- Measurements using Meso Scale Discovery V-Plex platform
- Rationale is that endothelial dysfunction early in cerebrovascular disease causes compensatory upregulation of endothelial & angiogenesis signaling
- 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:

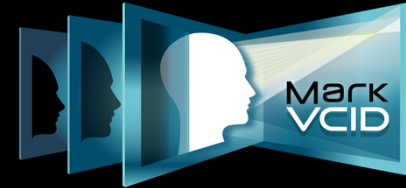
Endothelial Inflammatory Kit



- 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

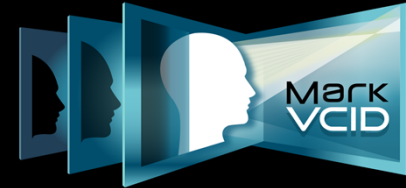


MarkVCID Biomarker Kits: Next Steps



- 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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