UCDAVIS HEALTH Alzheimer's Disease Research Center

NIH National Institute on Aging Designated Alzheimer's Disease Research Center

Update on Vascular Cognitive Impairment

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Disclosures

- Novartis
  - Executive Committee on a safety study of heart failure treatment
- Eisai
  - Consultant to Lecanemab trail for Alzheimer's Disease
- Nova Nordisc
  - Consultant to GLP-1 trial for Alzheimer's and mixed vascular dementia

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Overview

- What we know
- What we don't know
- Where are we going?

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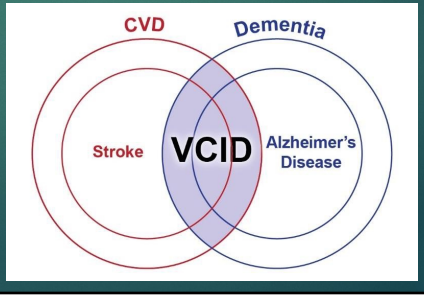
What We Know

- Vascular Cognitive Impairment is any disorder in which vascular disease contributes to cognitive impairment at all levels
  - Vascular disease may be primary
  - Vascular disease may contribute (eg. with Alzheimer's disease)

Gorelick et al, Stroke 2011



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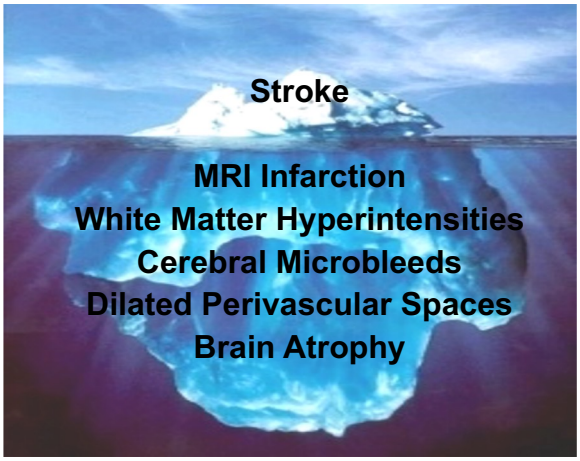
What We Know

- There is a spectrum of cerebrovascular brain injury



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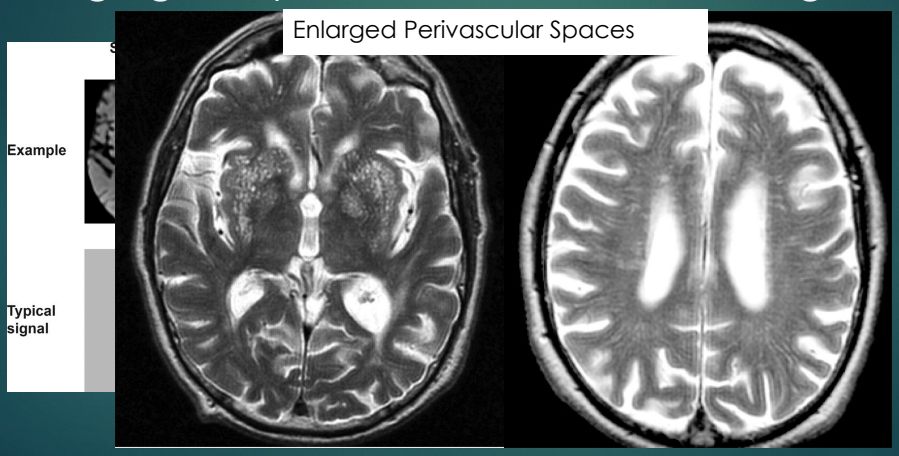
What We Know

Imaging is important to the clinical diagnosis of VCID



Vemuri, et al. Stroke, 2022

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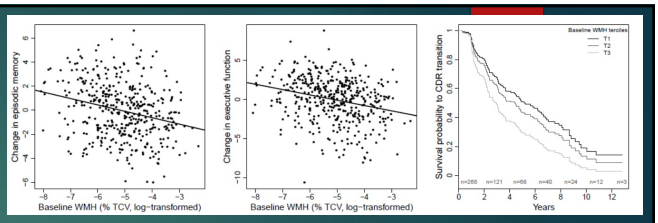
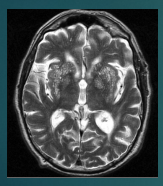
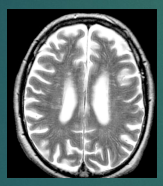
What We Know (cross-sectionally)



- WMH, infarcts and CMBs associate with cognition, particularly among non-demented individuals
- Enlarged perivascular spaces do not





Cognitive test	Model A (clinical)	p	Model B (clinic-radiological)	p
	Presence of ≥1 CMB(s) (vs. absence)			
BMET total score	−25.5 (−37.0, −14.0)	<0.001*	−13.0 (−25.3, −0.6)	0.040*
O/M subscore	−3.4 (−6.7, 0.0)	0.051	−0.4 (−4.0, 3.2)	0.826
EF/PS subscore	−8.4 (−11.6, −5.1)	<0.001*	−5.8 (−9.3, −2.2)	0.001*
	CMBs total count			
BMET total score	−19.3 (−25.4, −13.2)	<0.001*	−13.1 (−19.8, −6.4)	<0.001*
O/M subscore	−1.4 (−3.8, 0.9)	0.233	−2.1 (−4.0, 0.1)	0.115
EF/PS subscore	−5.6 (−7.3, −3.8)	<0.001*	−4.3 (−6.2, −2.4)	<0.001*
	CMBs ≥5			
BMET total score	−30.6 (−67.1, −34.1)	<0.001*	−36.6 (−53.7, −19.4)	<0.001*
O/M subscore	−9.6 (−14.4, 4.8)	<0.001*	−6.5 (−11.6, −1.5)	0.012
EF/PS subscore	−13.9 (−18.6, −9.2)	<0.001*	−10.7 (−15.6, −5.8)	<0.001*

	Demographic Characteristic			Neuroimaging Marker of Pathologic Change						
				Infarct						
Stage	Age	Female Sex	Educational Level	Cortical Gray Matter	Subcortical Gray Matter	White Matter	Other	Number (0, 1, or >1)	WMH Volume	Aβ, Global PiB Index
				Verbal Memory						
1	−.11	.06	.24							
2				−.06	−.29[b]	−.06	−.02	−.19	.02	−.18
3	−.24	−.02	.16		−.34[b]				.19	−.08
				Nonverbal Memory						
1	−.27[b]	.28[b]	.36[c]							
2				.06	−.36[c]	.05	−.05	−.13	−.08	−.27[b]
3	−.31[b]	−.21	.45[d]		−.23				.02	−.12
				Executive Function						
1	−.01	.08	.51[d]							
2				−.47[d]	−.33[b]	−.17	−.20	−.14	−.21	−.15
3	−.08	−.19	.38[c]	−.54[c]					.05	−.04

Maillard et al, Neurology, 2019
Marchant et al, JAMA Neurology, 2013
Nannoni et al, Journal of Stroke, 2021
Hilal et al, Neurology, 2018

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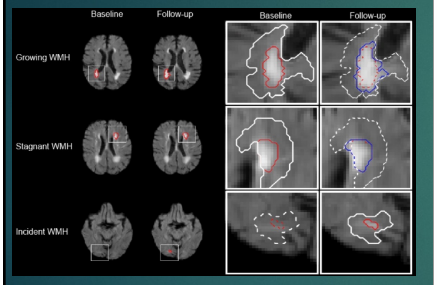
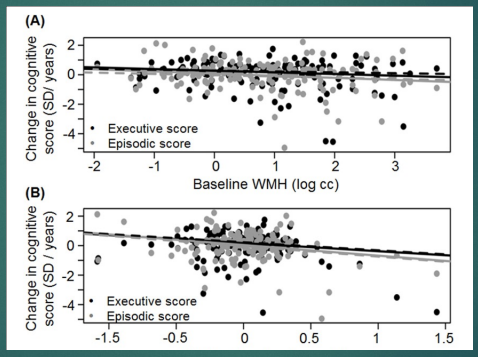
What We Know (Longitudinally)

Maillard et al, Neurology, 2012
Maillard et al, Stroke, 2014





	Rate of change in episodic memory		Rate of change in executive function	
Model and WMH measures	β	p Value	β	p Value
Primary model not adjusted for age				
Baseline WMH	−0.14	0.058[b]	−0.11	0.13
WMH extension	−0.72	0.0057[b]	−0.55	0.027[b]
WMH emergence	0.27	0.39	0.46	0.13
Final model not adjusted for age				
Baseline WMH	−0.16	0.045	NA	NA
WMH extension	−0.78	0.0046	NA	NA
Primary model adjusted for age				
Baseline WMH	−0.08	0.27	−0.06	0.43
WMH extension	−0.70	0.0053[b]	−0.55	0.022[b]
WMH emergence	0.19	0.54	0.37	0.21

- WMH, infarcts and CMBs associate with change in cognition, particularly in non-demented individuals

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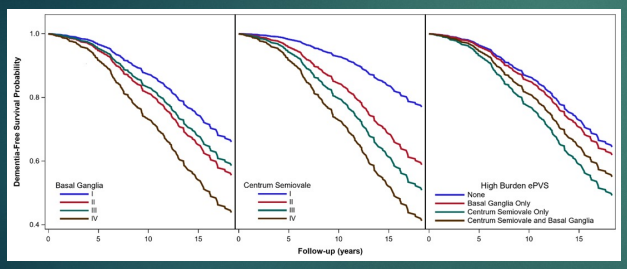
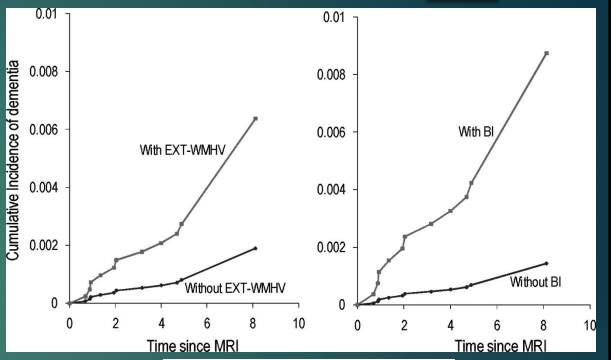
What We Know (Incident Dementia)

- WMH, infarcts, CMBs and EPVs associate with incident dementia





CMB location	All-cause dementia Model 1, HR (95% CI)
Any	1.74 [1.00–3.01] $p = 0.049$
Lobar only	1.01 [0.46–2.23] $p =$ n.s.
Lobar + mixed	1.48 [0.79–2.78] $p =$ n.s.
Deep only	2.50 [1.00–6.30] $p = 0.05$
Deep + mixed	2.99 [1.52–5.90] $p = 0.002$

Debette et al, Stroke, 2010
Romero et al, Neurobiology of Aging, 2017
Romero et al, underreview

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What we have recently learned

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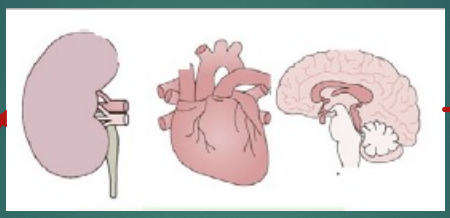
Concept: Vascular Remodeling and end organ injury

Arterial Stiffness

Hypertension
Atherosclerosis



End Organ Injury

Clinical Disease

Vasan et al, J Am Heart Assoc, 2019
Vasan et al, Hypertension, 2022

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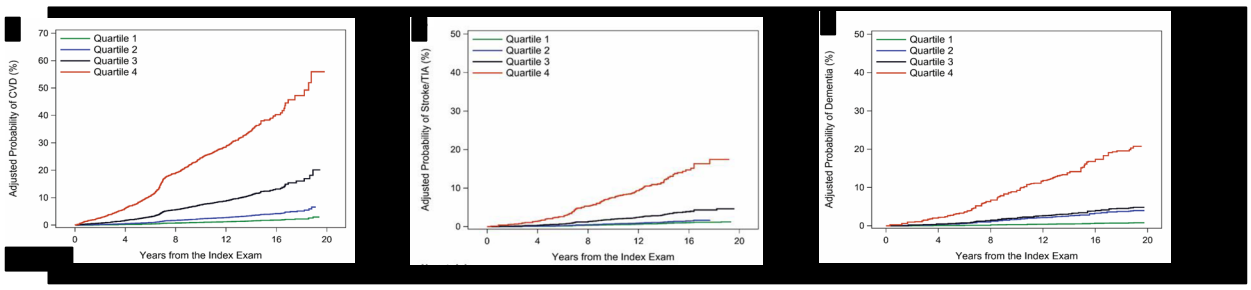
Clinical Consequents of Vascular Remodeling

- Vasan et al, Hypertension, 2022



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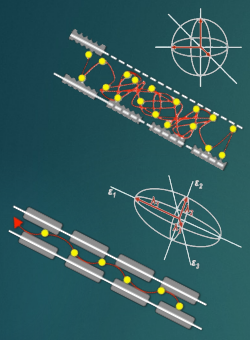
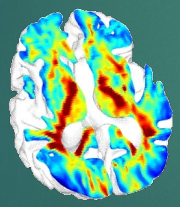
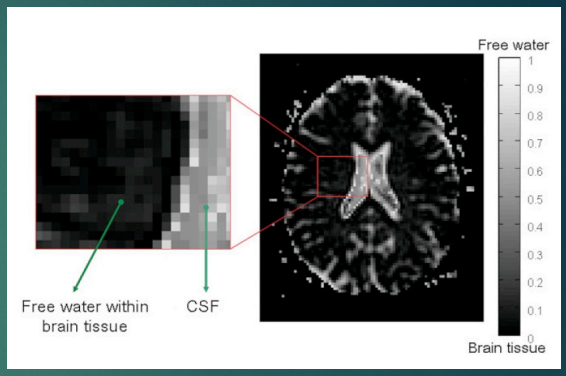
Free Water, a newer measure of vascular disease

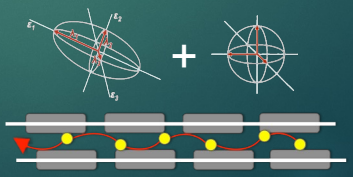
Pasternak et al, MR in Medicine, 2009







Water molecule
Axon + myelin
Injured axon + myelin
Axonal loss



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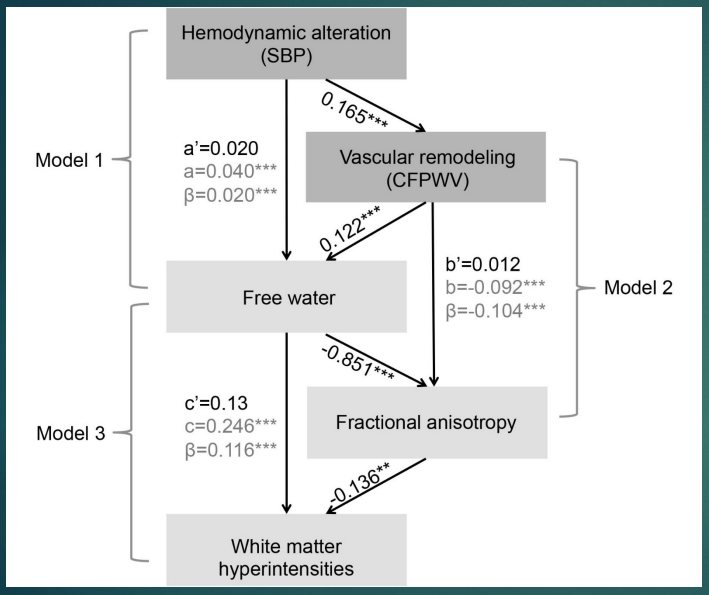

Vascular remodeling Free water and WMH Formation

Maillard et al, Stroke, 2016

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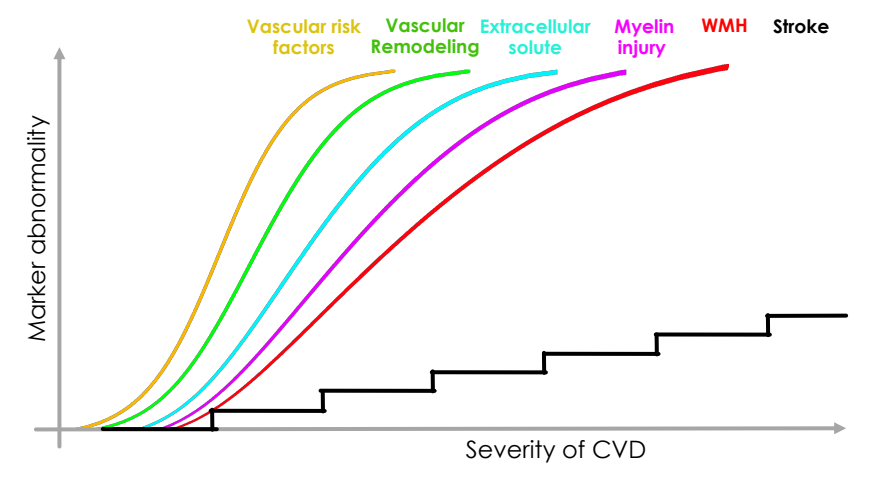
What we propose



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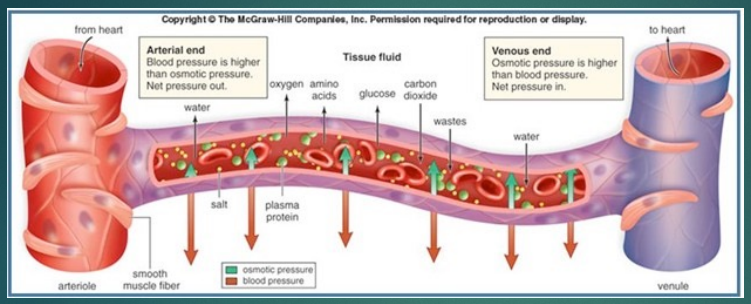
What we don't know



? ?

Vascular Remodeling → **Extracellular solute** → **Myelin injury**

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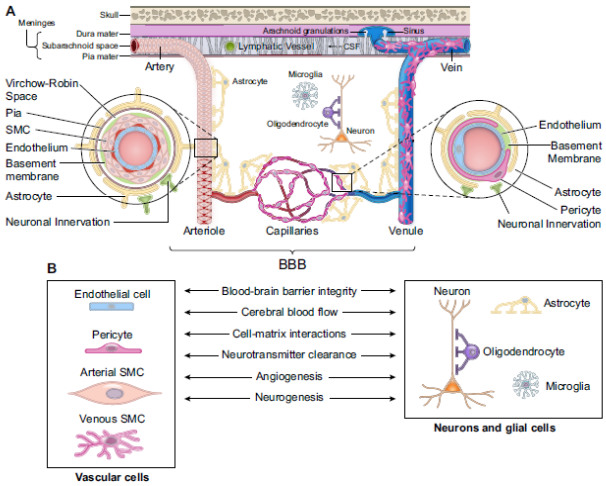

Where are We Going?

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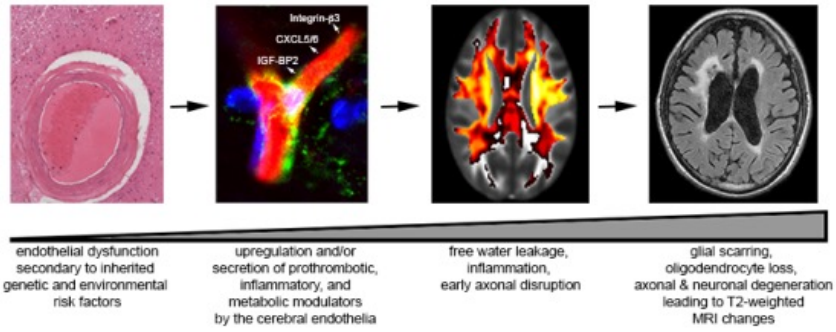

Working Hypothesis

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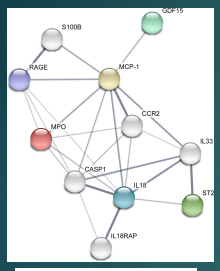
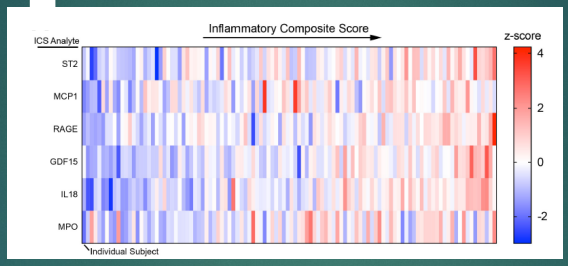
An IL-18-centered inflammatory network as a biomarker for cerebral white matter injury

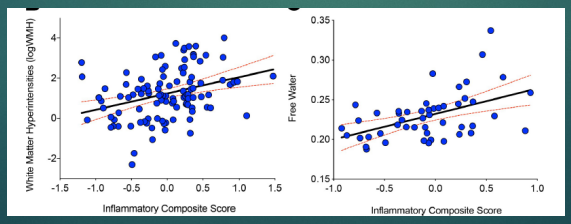
Marie Altendahl[1], Pauline Maillard[2], Danielle Harvey[3], Devyn Cotter[1], Samantha Walters[1], Amy Wolf[1], Baljeet Singh[2], Visesha Kakarla[4], Ida Azizkhanian[5], Sunil A. Sheth[6], Guanxi Xiao[4], Emily Fox[1], Michelle You[1], Mei Leng[7], David Elashoff[7], Joel H. Kramer[1,8], Charlie Decarli[2], Fanny Elahi[1], Jason D. Hinman[4]*

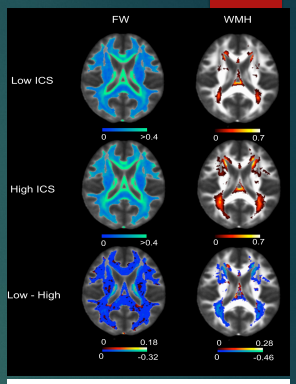
PLOS ONE



Inflammatory network.







Association of ICS with WMH and FW.

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NINDS VCID Studies

- Mark VCID
- Discovery
- Diverse VCID

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MarkVCID: A National Consortium Moving VCID Biomarkers Toward the Clinic

- Clinical trial-ready small vessel VCID biomarkers with high potential for positive impact in public health
- Established via *RFA-16-020, RFA-16-021*
- 7 project sites across the Unites States: CA, IL, KY, MD, MA, NM
- Coordinating Center at MGH

NIH National Institutes of Health

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National Institute on Aging

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POLICY FORUM

MarkVCID cerebral small vessel consortium: I. Enrollment, clinical, fluid protocols

Donna Wilcock[1] | Gregory Jicha[1] | Deborah Blacker[2] | Marilyn S. Albert[3] | Lina M. D'Orazio[4] | Fanny M. Elahi[5] | Myriam Fornage[6] | Jason D. Hinman[7] | Janice Knoefel[8] | Joel Kramer[7] | Richard J. Kryscio[1] | Melissa Lamar[9] | Abhay Moghekar[3] | Jillian Prestopnik[10] | John M. Ringman[4] | Gary Rosenberg[10] | Abhay Sagare[11] | Claudia L. Satizabal[12] | Julie Schneider[9] | Sudha Seshadri[12] | Sandeepa Sur[13] | Russell P. Tracy[14] | Sevil Yasar[15] | Victoria Williams[16] | Herpreet Singh[17] | Lidiya Mazina[18] | Karl G. Helmer[19] | Roderick A. Corriveau[20] | Kristin Schwab[17] | Pia Kivisäkk[21] | Steven M. Greenberg[17] | for the MarkVCID Consortium

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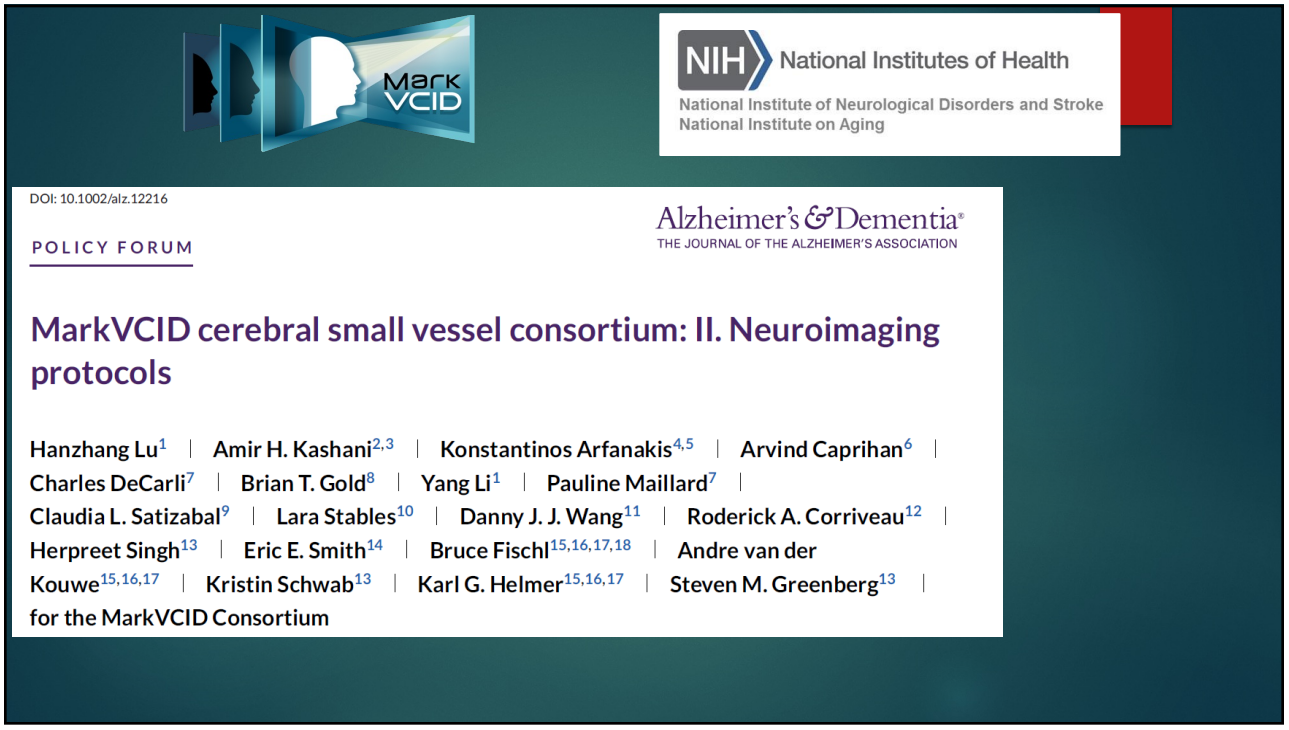
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National Institute on Aging
DOI: 10.1002/alz.12216
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MarkVCID cerebral small vessel consortium: II. Neuroimaging protocols
Hanzhang Lu[1] | Amir H. Kashani[2,3] | Konstantinos Arfanakis[4,5] | Arvind Caprihan[6] | Charles DeCarli[7] | Brian T. Gold[8] | Yang Li[1] | Pauline Maillard[7] | Claudia L. Satizabal[9] | Lara Stables[10] | Danny J. J. Wang[11] | Roderick A. Corriveau[12] | Herpreet Singh[13] | Eric E. Smith[14] | Bruce Fischl[15,16,17,18] | Andre van der Kouwe[15,16,17] | Kristin Schwab[13] | Karl G. Helmer[15,16,17] | Steven M. Greenberg[13] | for the MarkVCID Consortium

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Diverse VCID
Diverse VCID:
White Matter Lesion
Etiology of Dementia
in Diverse Populations

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GOAL: predict the impact of progressive white matter injury—including location and specific amounts of WMH—on cognition using a precision medicine approach in a large and diverse clinical population

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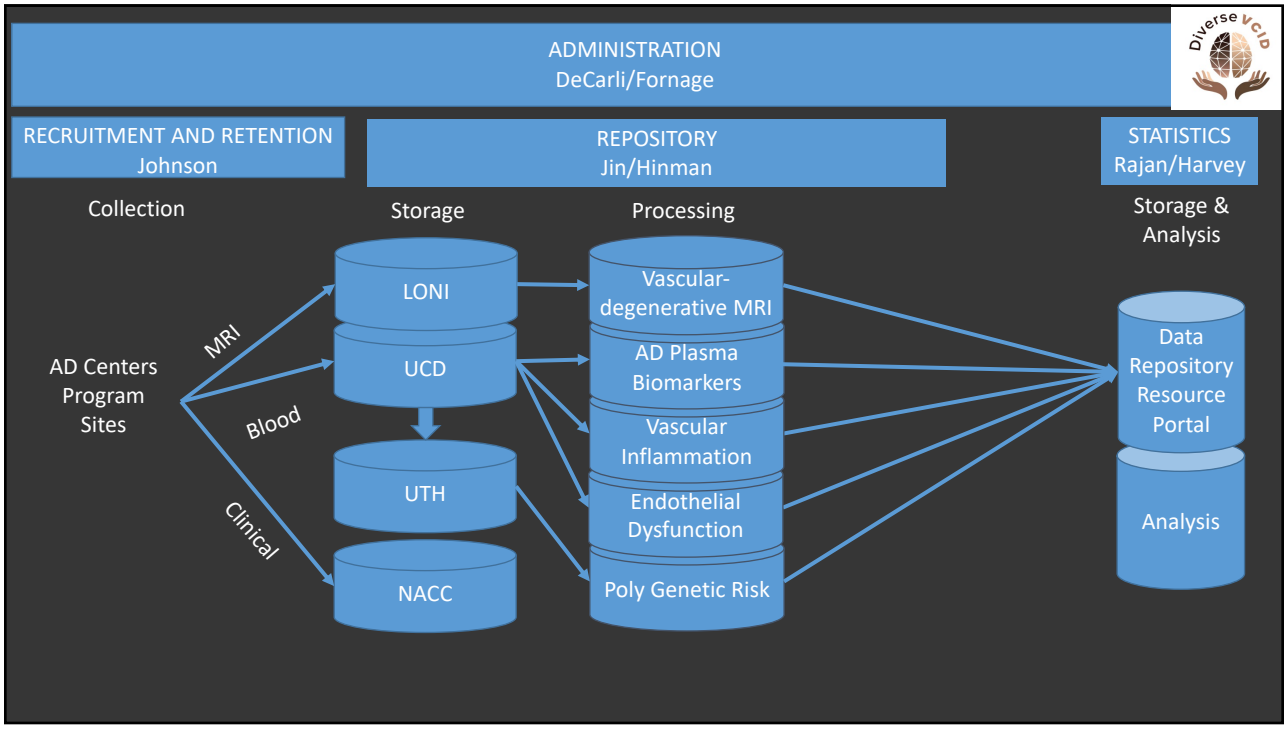

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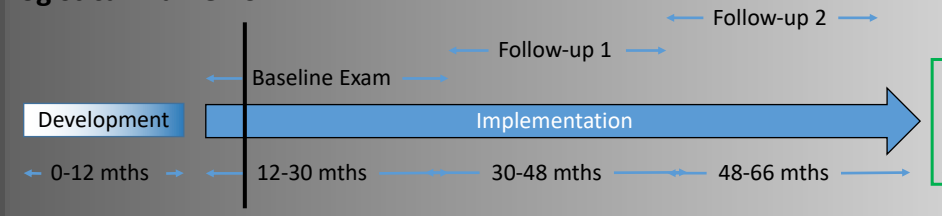
Logistical Framework



Clinical progression
Cognitive trajectories
WM injury progression
Stroke, MI and Death

IRB
SOPs
Site Selection
Training

Enrollment (N=2250)
Inclusion:
Cognitive Complaint
Incidental WMH
33% Black, Hispanic, White
Exclusion:
Stroke, cortical MR infarcts, dementia

3 assessments at 18 month intervals
UDS with enhanced Cognition
Framingham Cardiovascular Risk
Vascular health history questionnaire
Life's simple 7 assessment
Clinical laboratories
Blood for plasma/DNA
MRI
Autopsy on select subset

Deliverable: A clinical risk score that predicts dementia based on neuroimaging, plasma biomarkers, genetic and clinical data

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Summary

Vascular Cognitive Impairment is a heterogeneous disorder of large and small vessels often co-occurring with degenerative diseases such as AD

Understanding of the association between systemic and brain vascular disease remains incomplete

Newer prospective studies are ongoing to investigate biomarkers and cognitive consequences of VCID forming the basis for future clinical trials

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