# The State of the field for fluid biomarkers of VCID

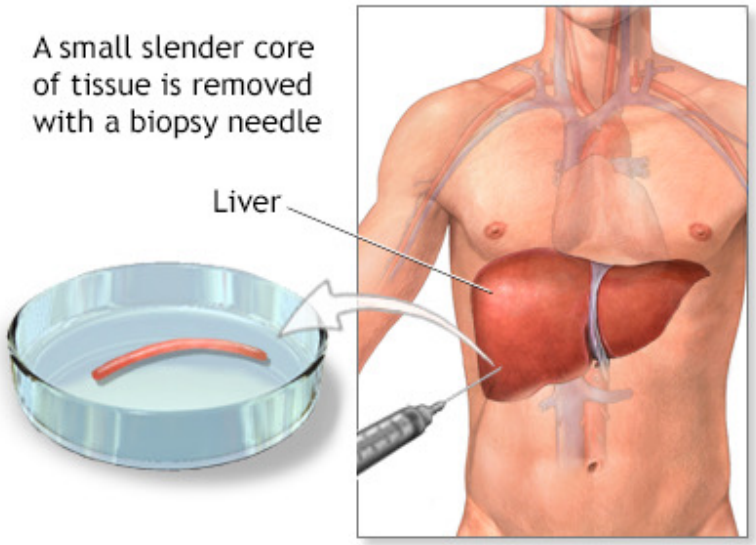
**Donna Wilcock Ph.D.**
Director, Center for Neurodegenerative Disorders
Professor of Neurology
Indiana University

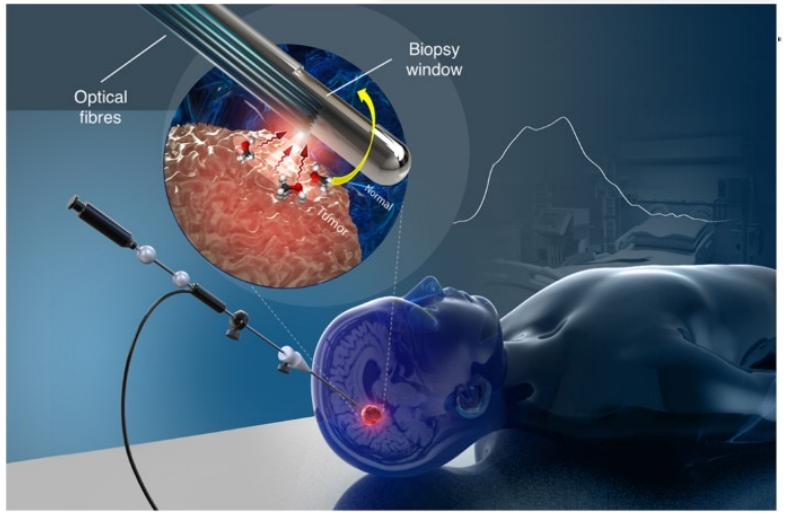
# Disclosures

- Nothing to disclose.

# The utility of biomarkers

A Biopsy would be ideal

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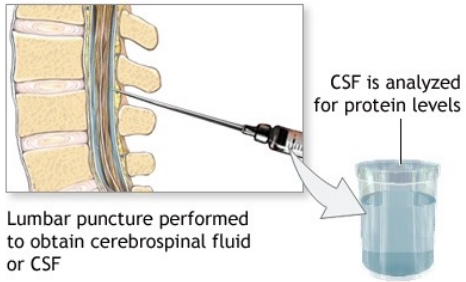
MRI / PET

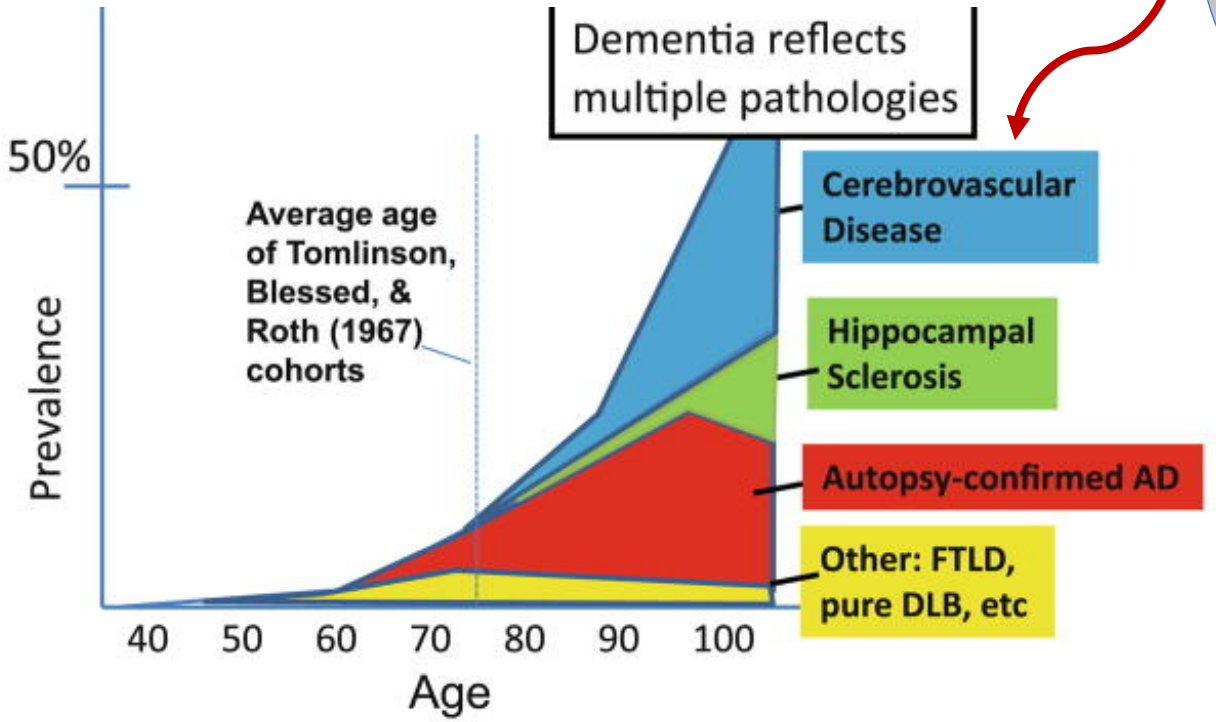
Spinal Fluid / Spinal Tap




Blood Collection

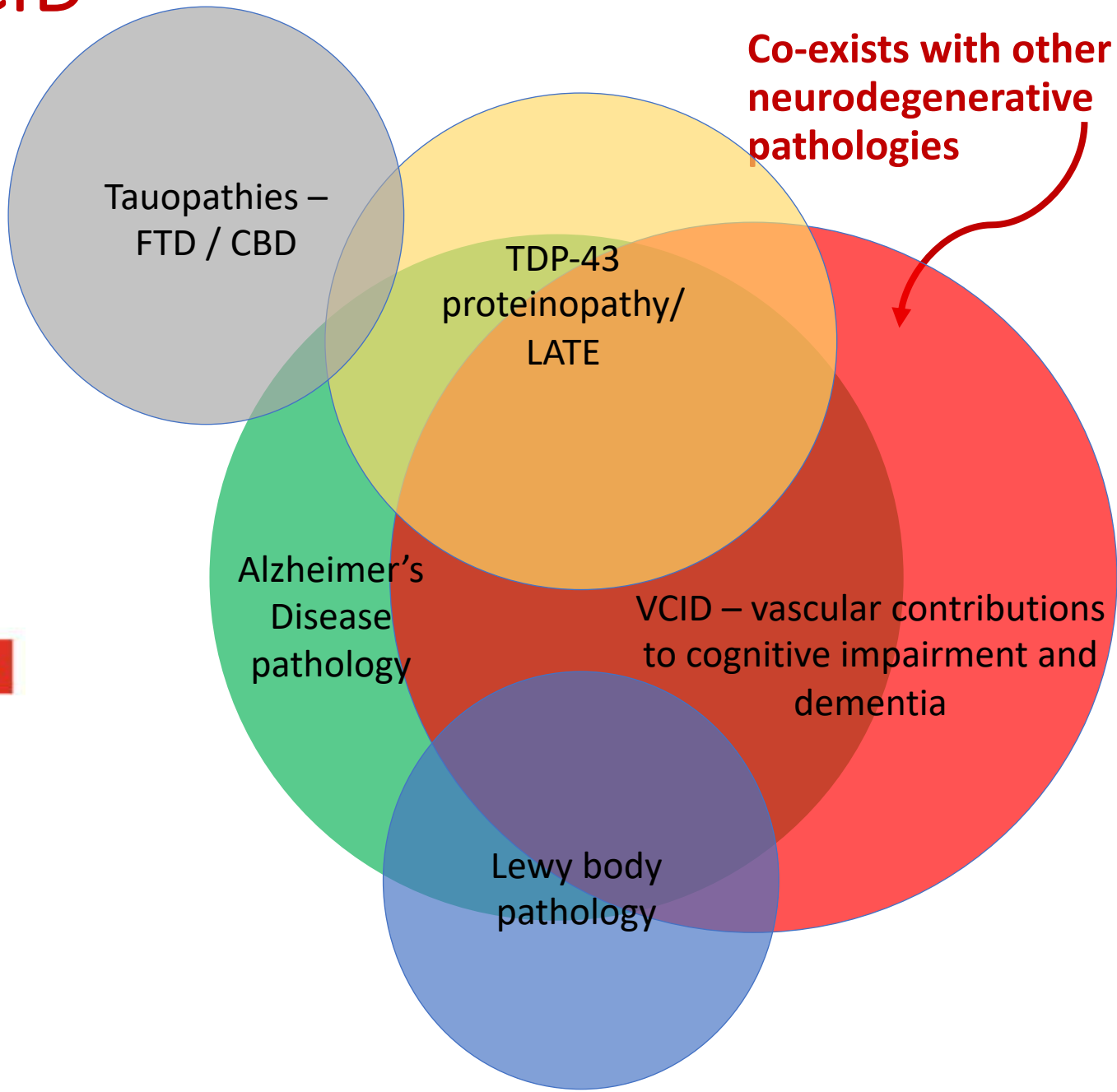
# VCID

**Very Common**

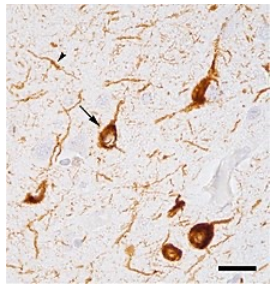


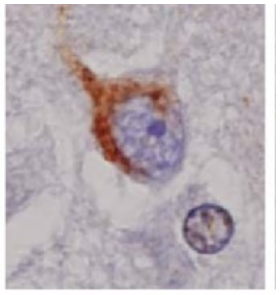

Nelson PT et. al. Acta Neuropathol. 2011

**Co-exists with other neurodegenerative pathologies**

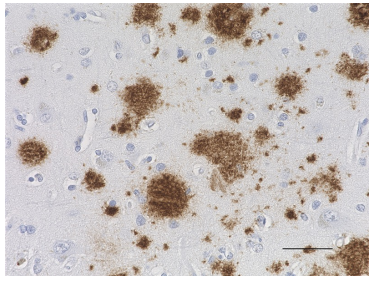


# The need for biomarkers

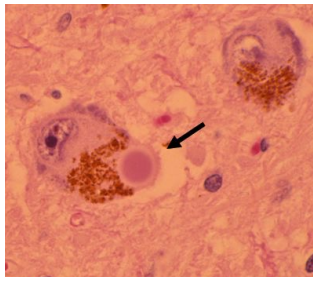




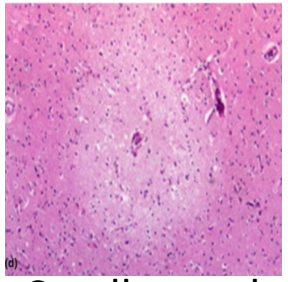
TDP-43



Beta-amyloid



Lewy body



Small vessel disease

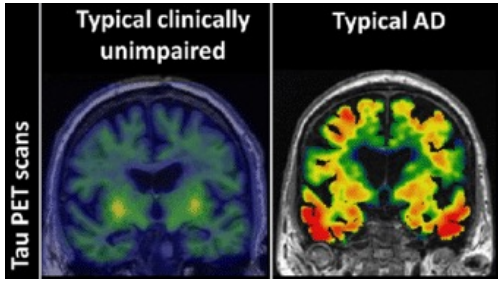
Plasma tTau
Plasma brain-derived tau
CSF MTBR-Tau-243
Tau-PET

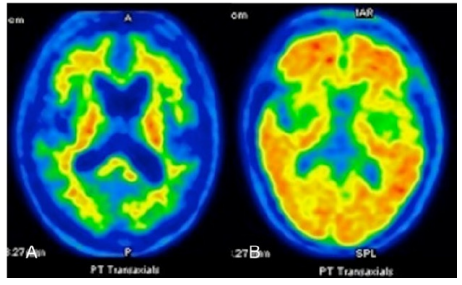
?

Plasma Aβ42/Aβ40
Plasma p-Tau181
Plasma p-Tau217
CSF Aβ42
CSF Aβ42/Aβ40
Amyloid-PET

?

?



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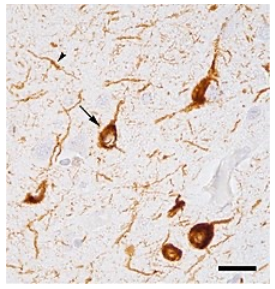

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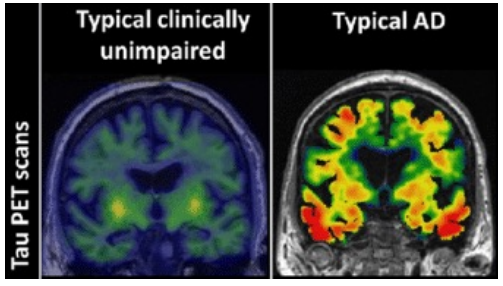


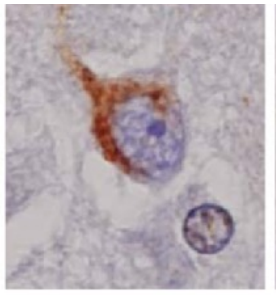

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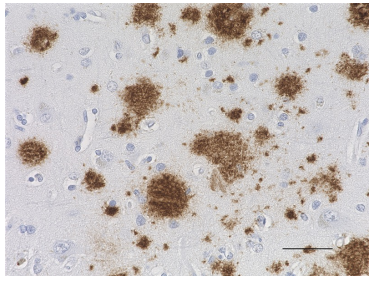

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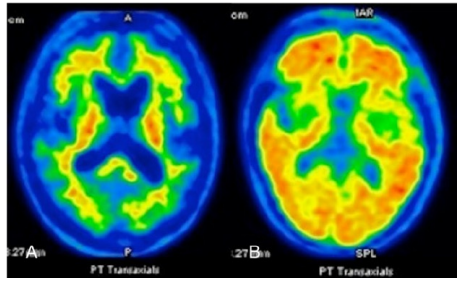

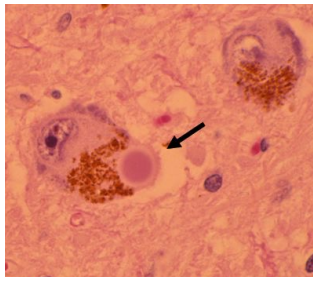

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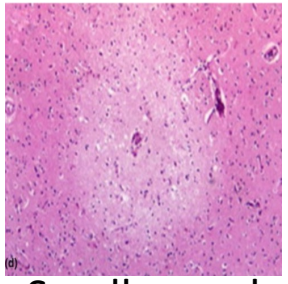

Small vessel disease

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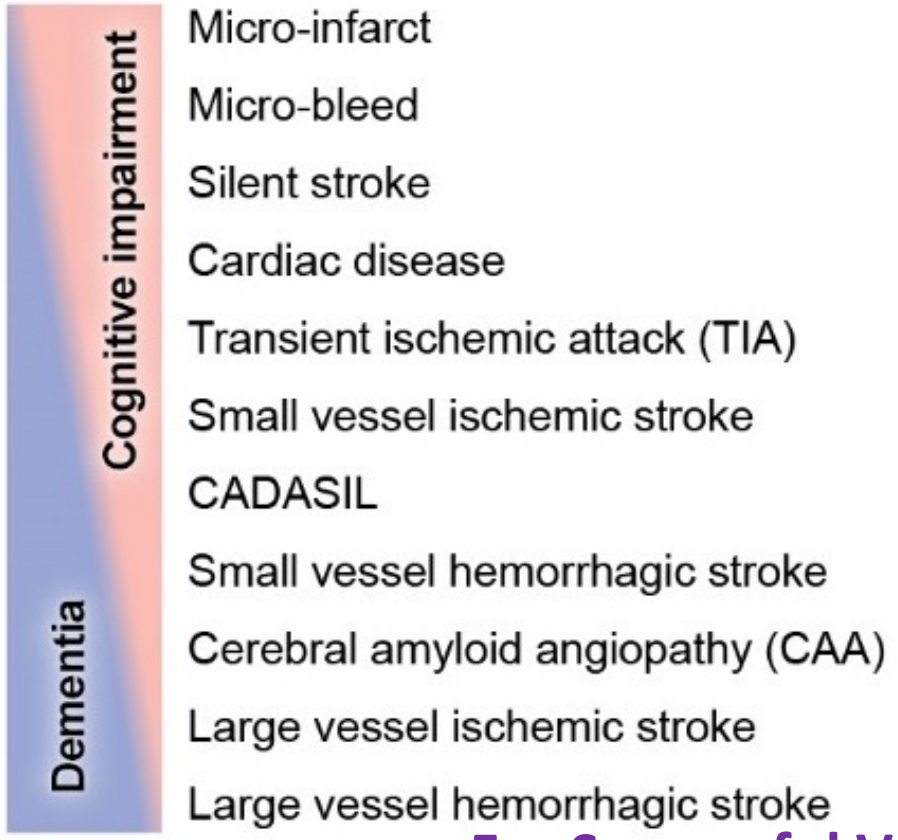
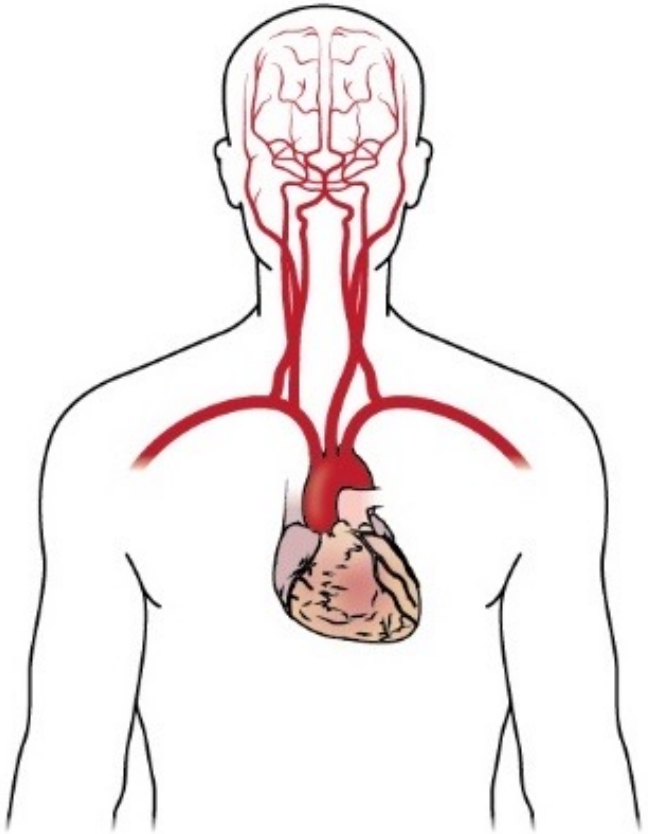
# VCID Reflects Varied Vascular Pathologies, and therefore Mechanisms



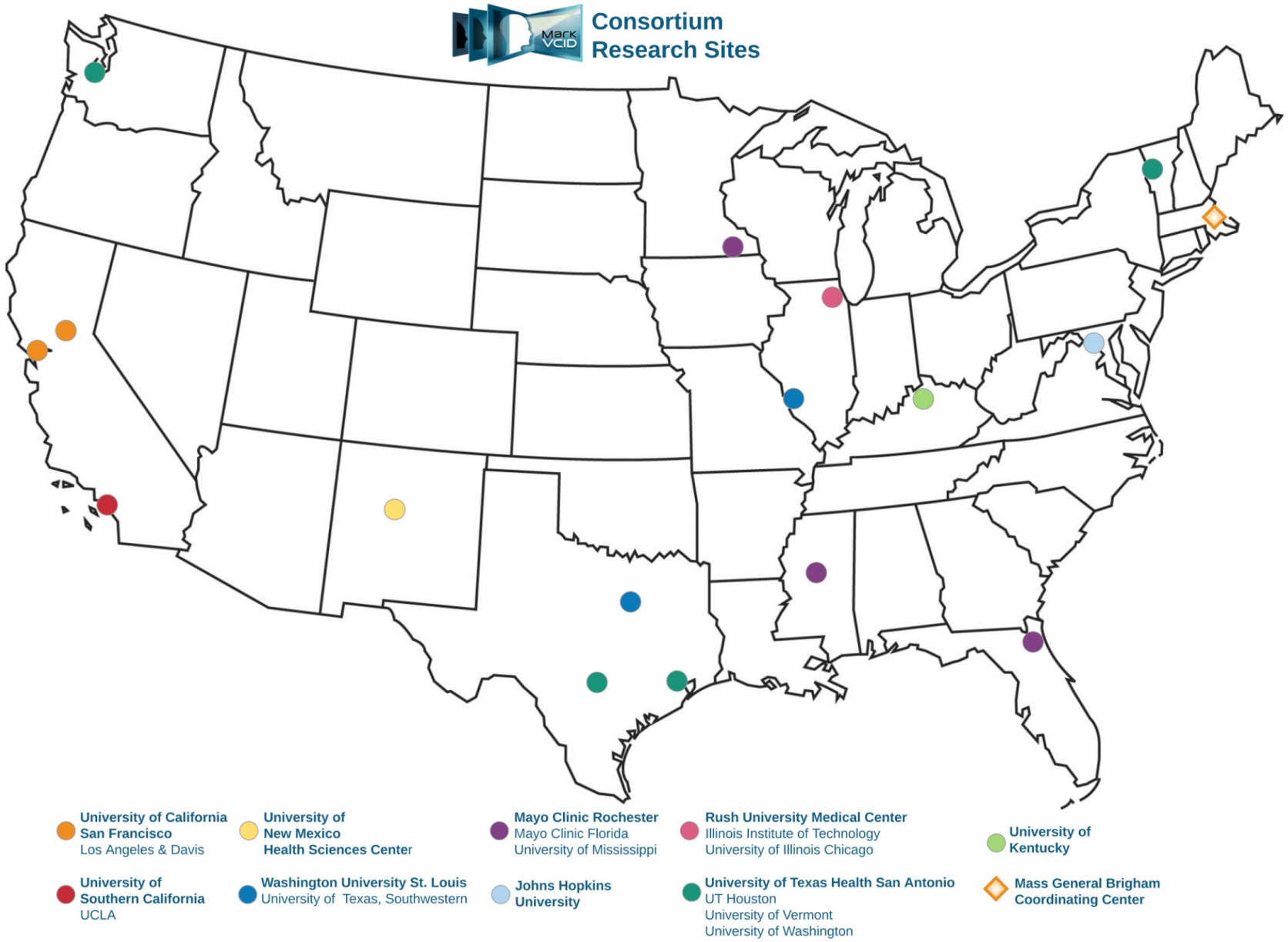



**Absolutely critical: Develop clinical outcomes & biomarker measures, and interventions, that match the targeted vascular injuries/disease.**

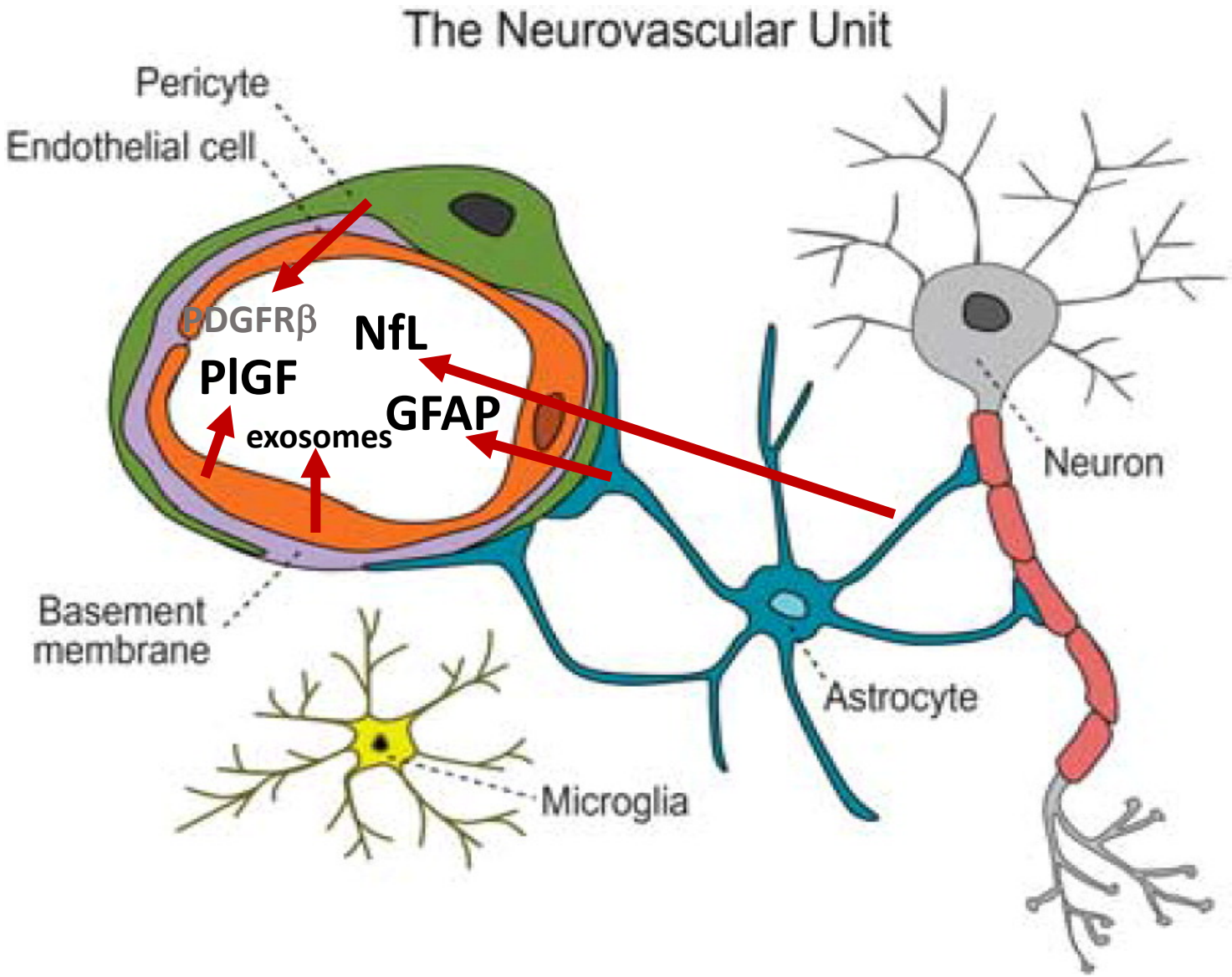
**For Successful VCID Intervention Advances are Needed On:**

- ✓ **Mechanisms**
- ✓ **Biomarkers**
- ✓ **Interventions**
- ✓ **Clinical Trials**

A national, NINDS consortium with the goal of identifying and validating novel biomarkers for diagnosis, prognosis, and stratification of VCID (primarily cerebral small vessel disease).

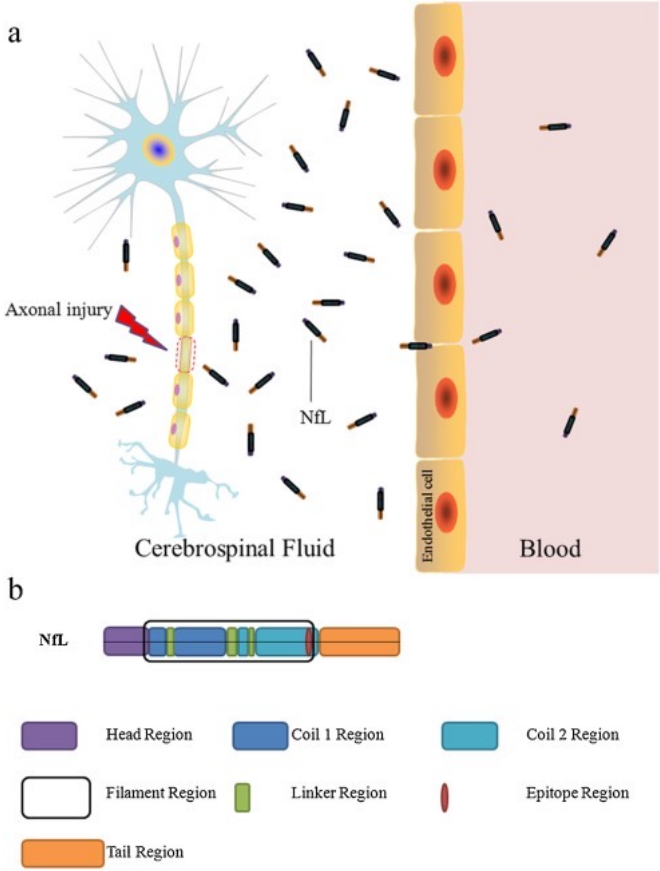


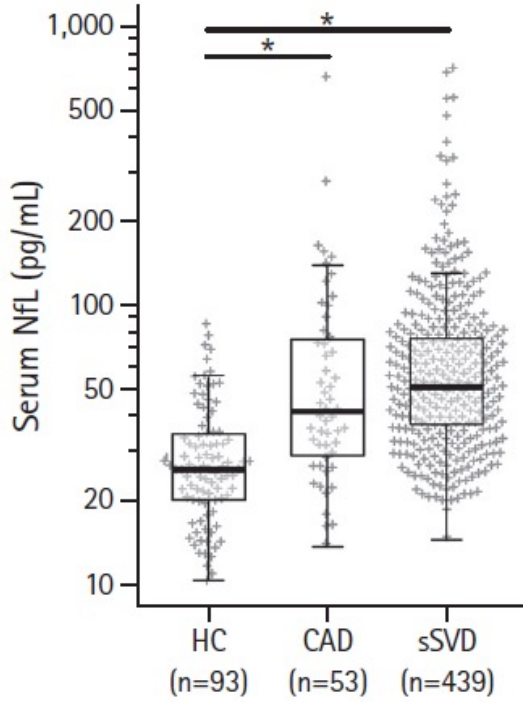
# Fluid biomarkers being explored in MarkVCID



# Plasma neurofilament light (NfL)

- **Primary hypothesis**: Elevated concentrations of NfL will be related to lower cognitive function
- **Primary biomarker category**: Susceptibility/Risk
- **Context of use**: Risk stratification for inclusion VCID trials
- Using Quanterix Simoa

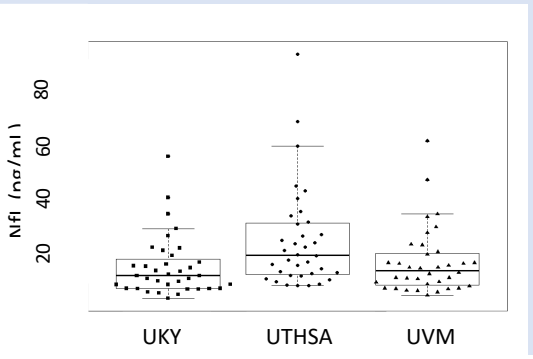


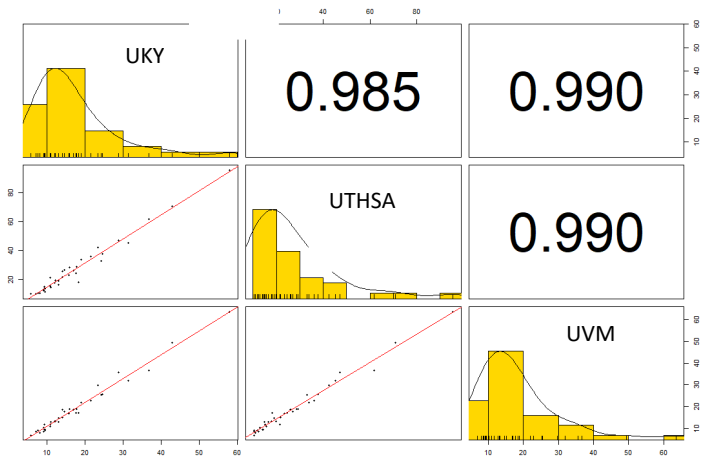



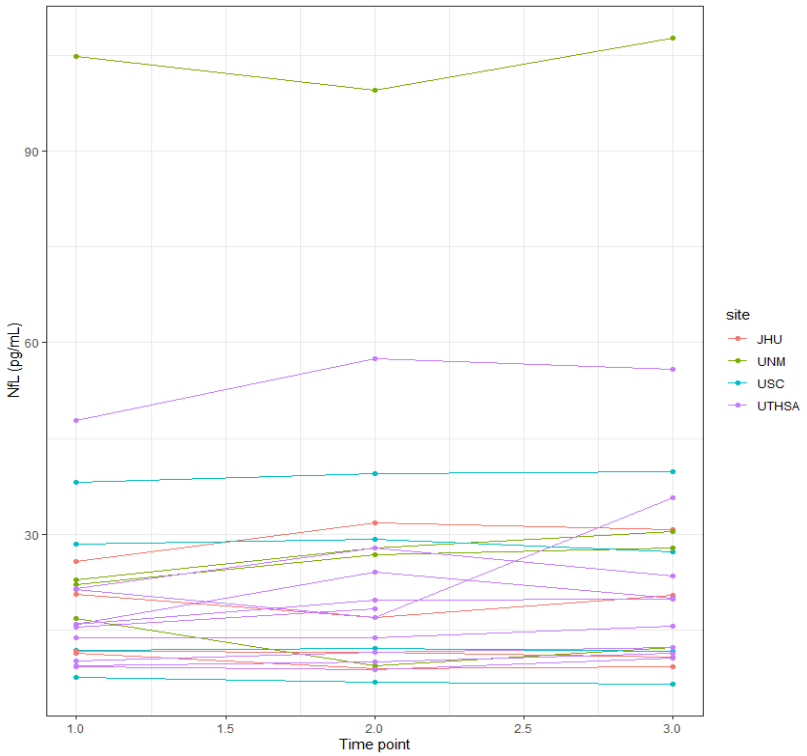

- ✓ Important a role in neuronal cytoskeleton and maintaining neuronal structure
- ✓ Released in axonal injury, increased levels (CSF, blood) correlate with several diseases with neuronal and axonal injury
- ✓ Blood and CSF NfL concentrations correlate strongly

# Plasma NfL MarkVCID validation

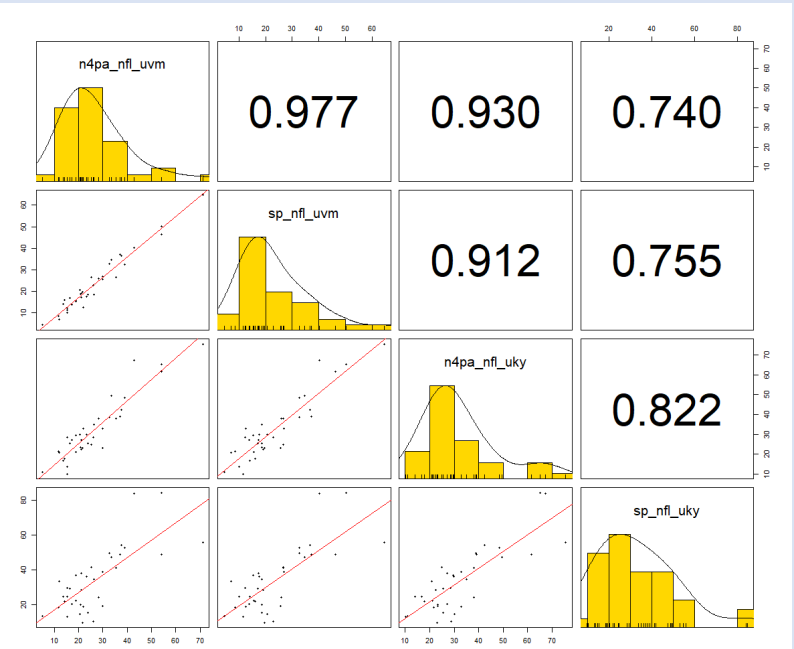
**Inter-site reproducibility**



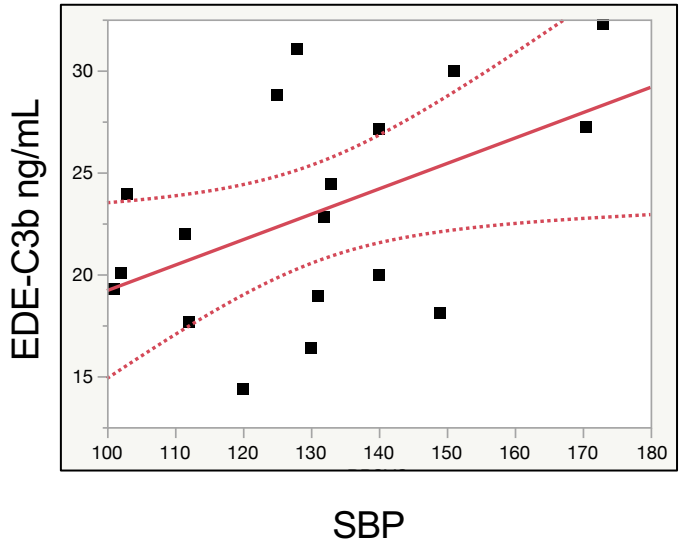

**Single-plex vs. N4PA**

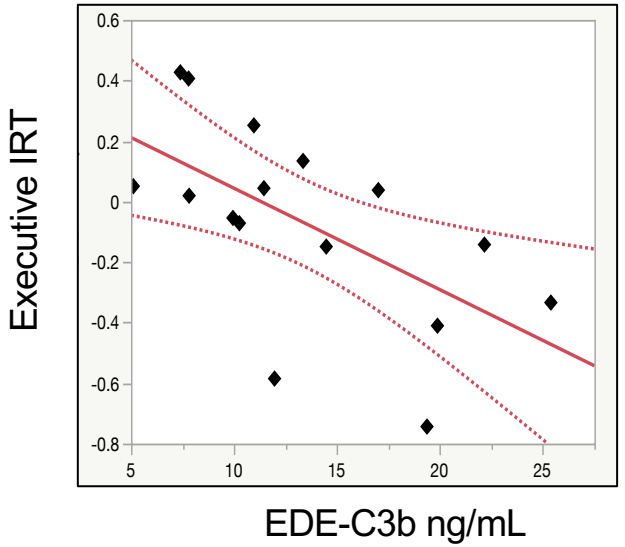



- ✓ **Intra-plate reliability: Overall CV = 4.11%**
- ✓ **Test-retest (x3 time-points within 30 days): ICC = 0.979**
- ✓ **Inter-site reproducibility: ICC = 0.91**
- ✓ **Results across single-molecule and N4PA are consistent: ICC ≥ 0.81**

# Plasma Endothelial-Derived Exosomes - Inflammation

- Endothelial-derived exosomal complement cargo (EDE-C3b and EDE-C1Q) reflect endothelial innate immune inflammation
- Levels of EDE-C3b and EDE-C1Q are elevated in individuals with WMH presumed of vascular etiology
- Positive association with systolic blood pressure and inverse association with executive function
- Context of Use: diagnostic classification in anti-inflammatory clinical trials

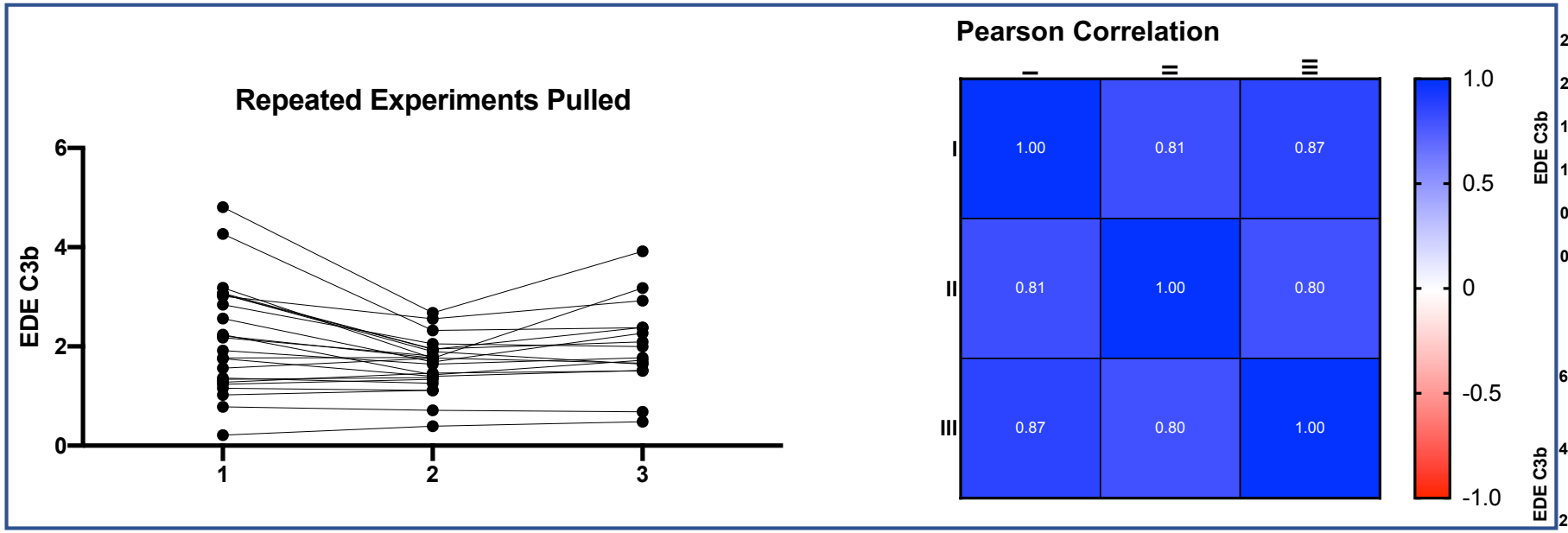



p=.01

# Plasma Endothelial-Derived Exosomes – Instrumental validation

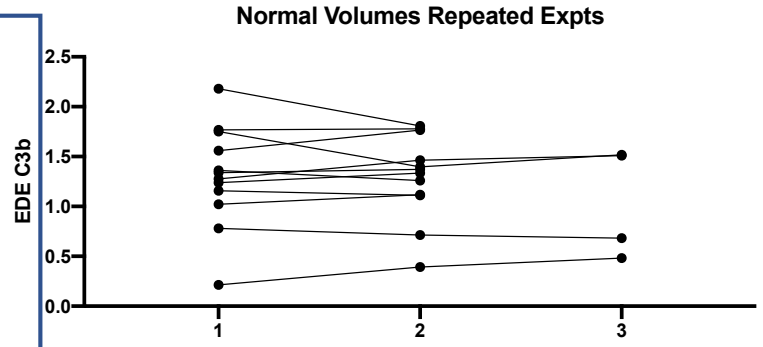
- ❑ Benchmark: ICC > 0.8
- ✓ Meeting success criterion: ICC > 0.82 (range 0.7 - 0.93)

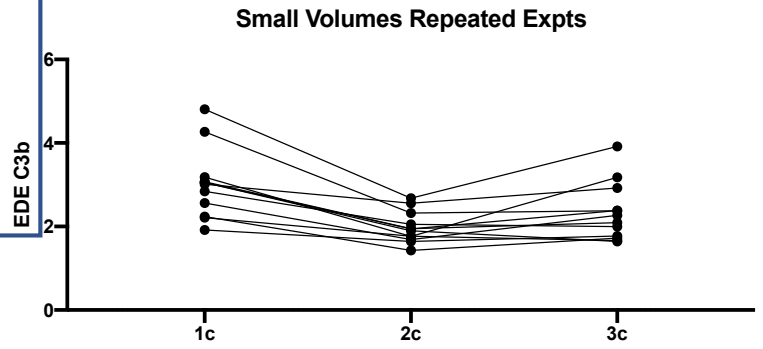






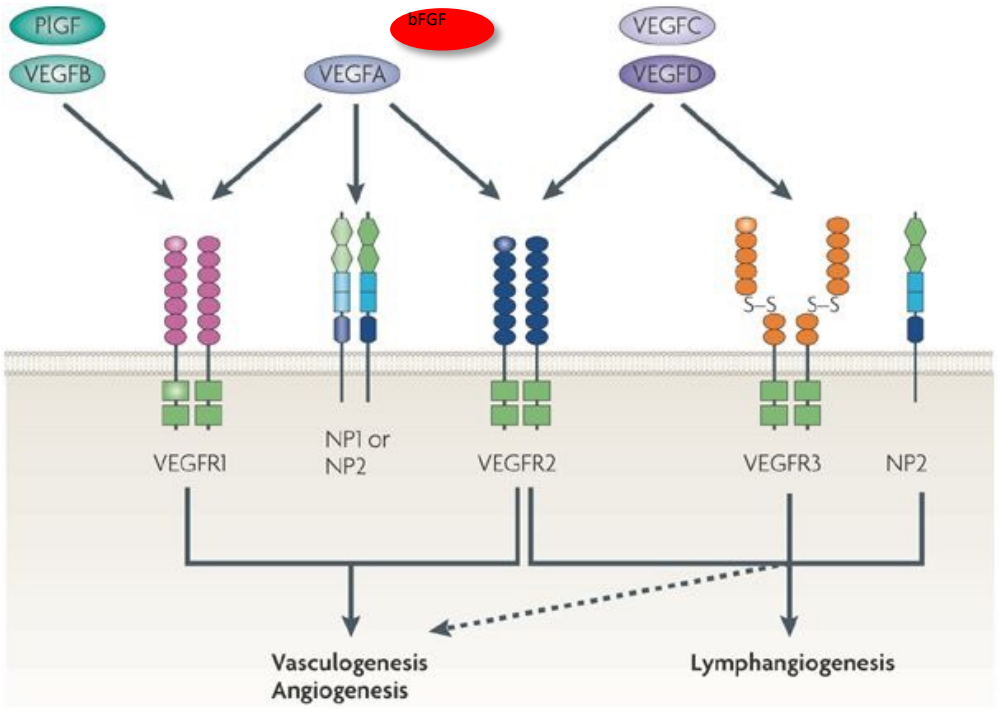
**Plasma Volume Matters**

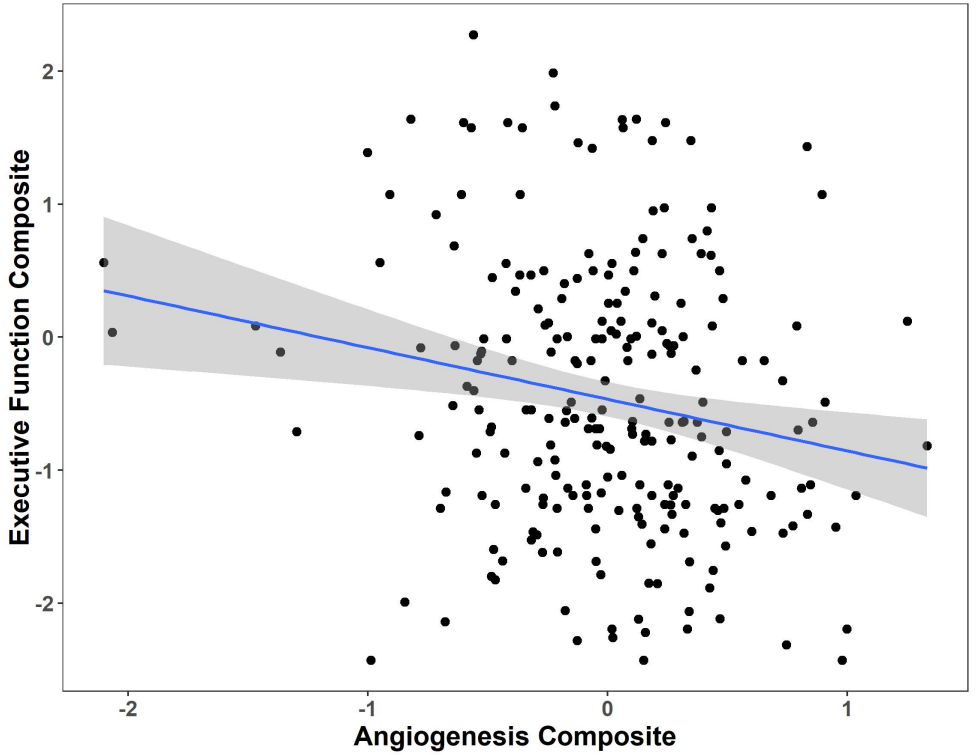


# Plasma Endothelial Signaling Kit

- bFGF, PlGF, VEGF-D are all pro-angiogenic factors
- Signaling drives proliferation and migration of endothelial cells
- Specific effect on cerebral endothelia is less understood
- Strong effect of composite on decline in executive function

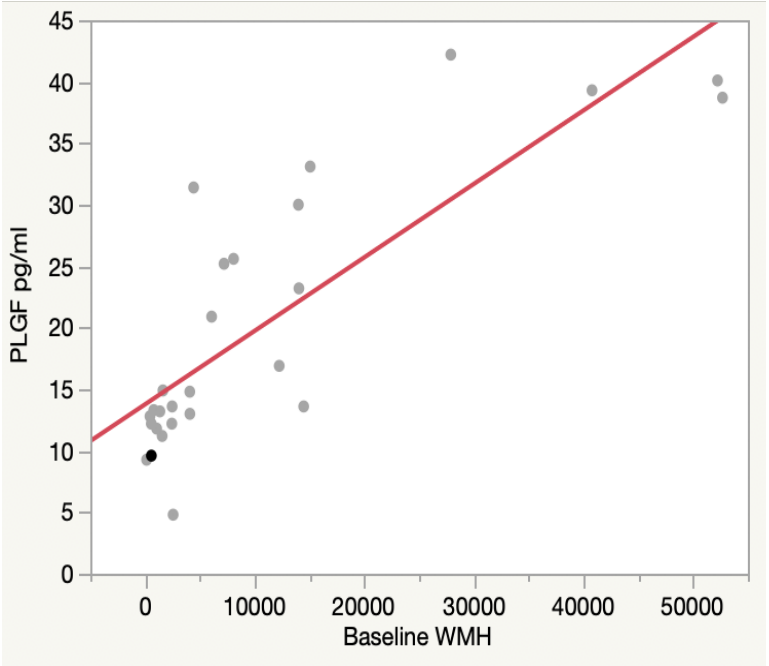


# CSF PlGF

- CSF Aβ and tau are established biomarkers of brain AD pathology.
- Neurofilament light (NfL) is a biomarker of neurodegeneration.
- We need a CSF biomarker for cerebral small vessel disease so we can add the “V” to “ATN”.
- PLGF has shown a strong relationship with cerebrovascular disease in both the UKY and UCSF cohorts.

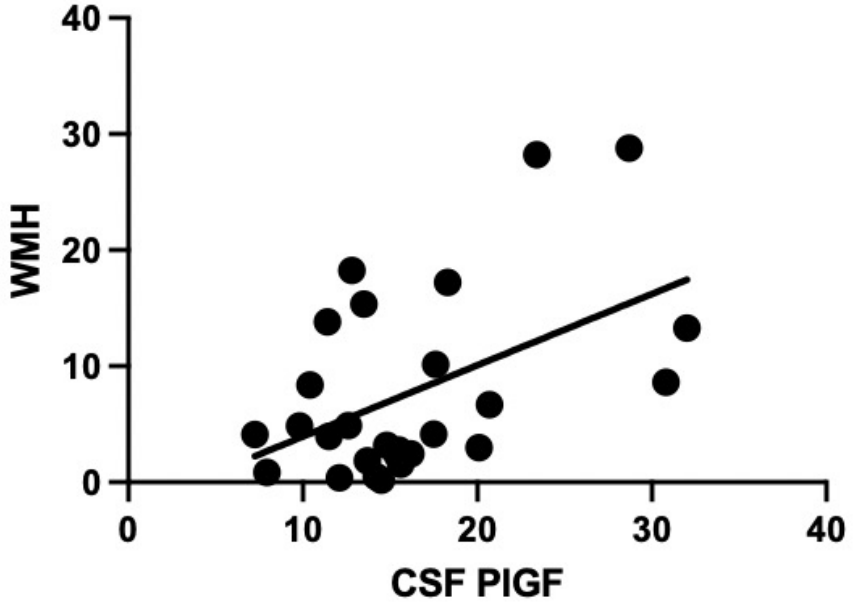
- Any clinical trial for C-SVD or AD requires confirmation that the targeted pathology is present, and requires assurance, where possible, that dementia-causing co-morbidities are minimal.
- This kit aims to add the “V” to “ATN” from a single CSF sample.



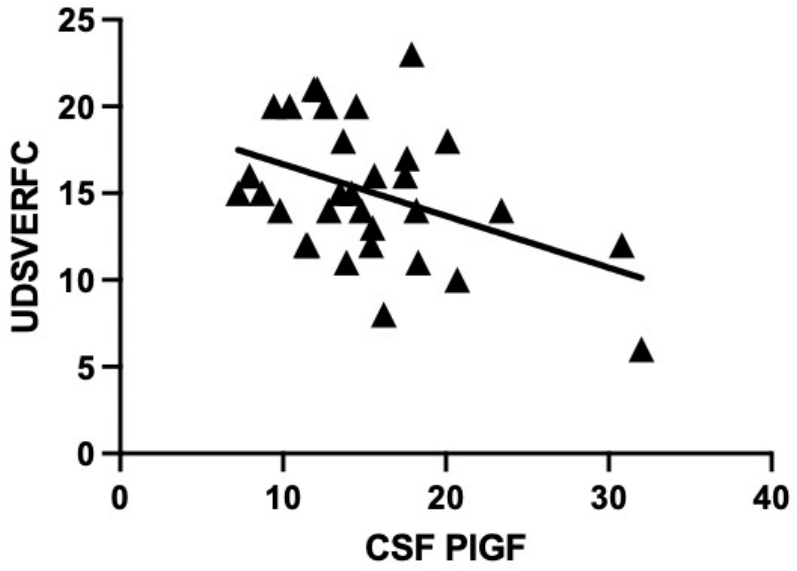
# CSF PlGF as a biomarker for cerebral small vessel disease

- PlGF is a member of the VEGF family.
- PlGF is weakly angiogenic when acting alone, but when part of a VEGF-A-PlGF heterodimer, can bind VEGFR2 and stimulate angiogenesis.
- PlGF deletion in mice leads to impaired angiogenesis in response to pathophysiological conditions such as ischemia.
- PlGF knockout mice are are viable and develop normally.

**CSF PIGF is associated with increased WMH volume**




**CSF PIGF is associated with worse verbal fluency scores**



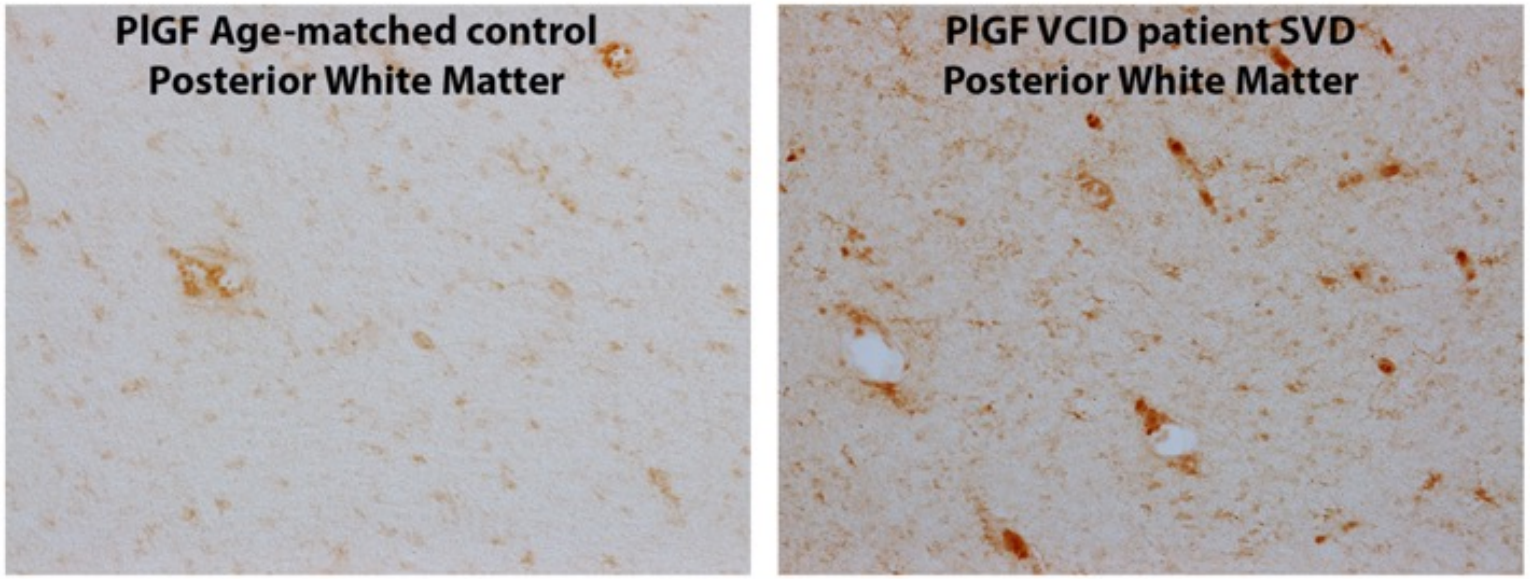
# CSF PLGF Instrumental Validation

- 10 CSF samples from UNM and 10 CSF samples from UKY were shipped to UCSF, UKY, and UTHSA for analysis using the Quanterix Simoa PlGF kit.
- Instrumental validation has been completed and successfully achieved the target.
- We pre-specified an ICC of 0.8 or greater as being acceptable as instrumental validation and we achieved an ICC of 0.94 across the three sites.

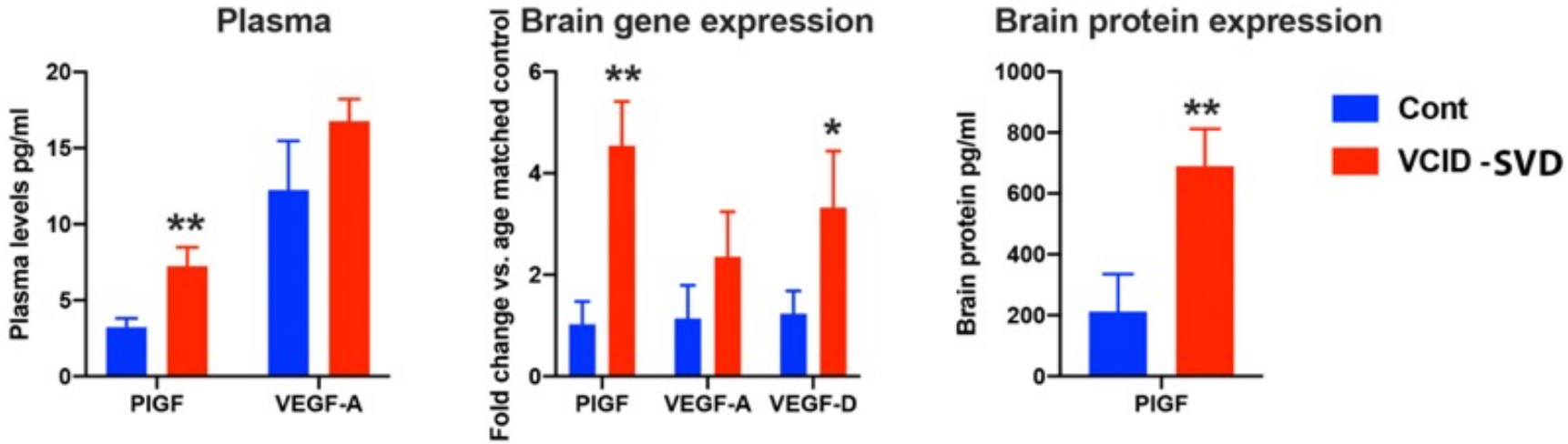
**Intraclass Correlation Coefficient**

| | Intraclass Correlation[b] | 95% Confidence Interval | | F Test with True Value .9 | | |
|---|---|---|---|---|---|---|
| | | Lower Bound | Upper Bound | Value | df1 | df2 |
| Single Measures | .940[a] | .866 | .975 | 1.711 | 19 | 24 |
| Average Measures | .979[c] | .951 | .991 | 4.853 | 19 | 25 |

# PlGF in the human brain

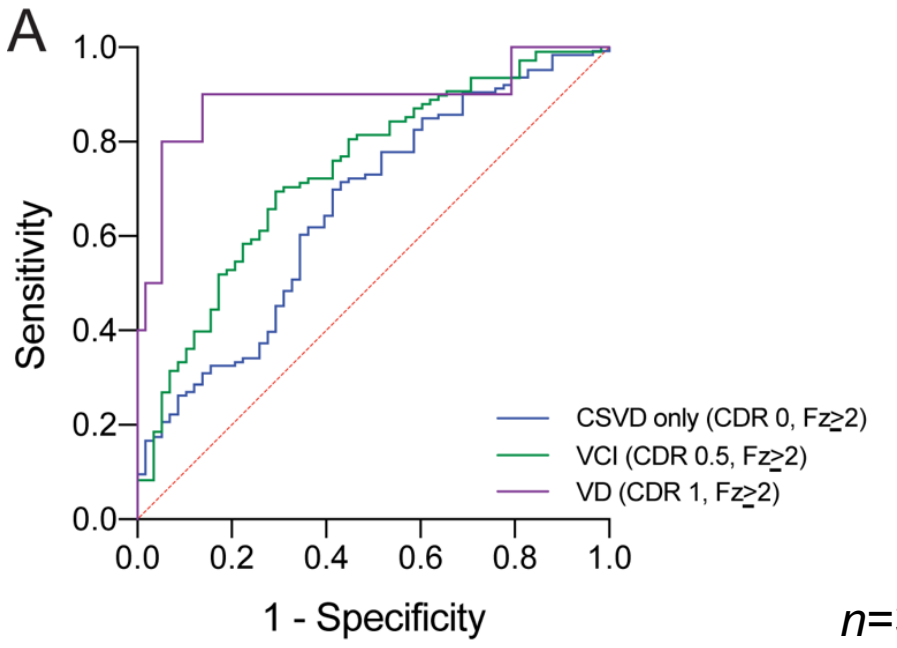



- N=12 / group matched for age, sex, and ApoE status



# Plasma Placental Growth Factor may be Diagnostic for VCID

ROC Curves Using CDR/Fazekas

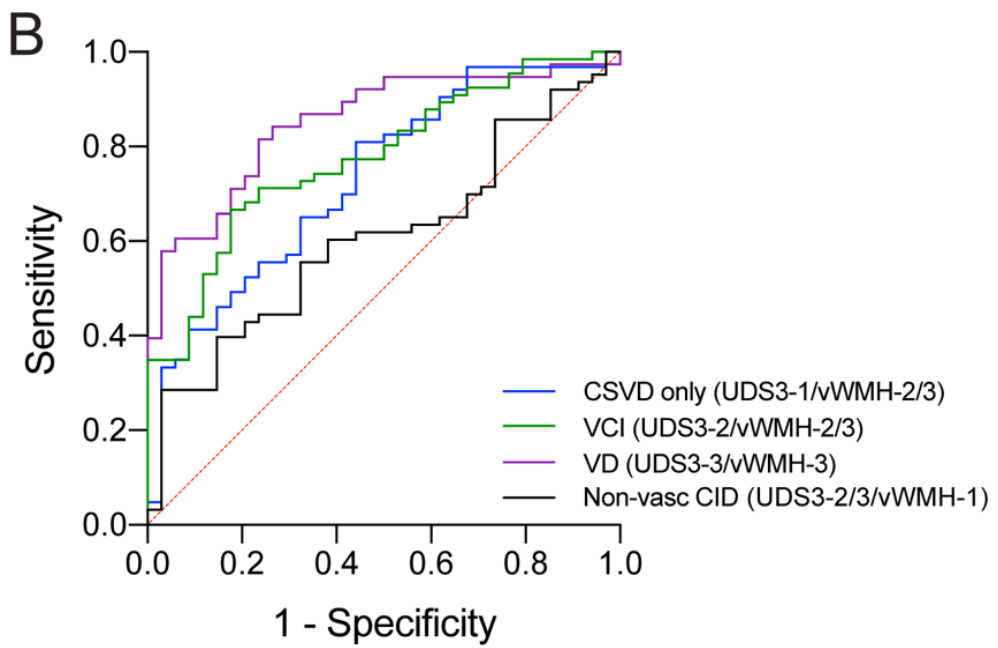



*n*=335

Diagnostic accuracy of Plasma PlGF:

- Vascular Dementia (CDR 1, Fazekas ≥2) = 0.89
- Vascular Cognitive Impairment (CDR 0.5, Fazekas ≥2) = 0.74

ROC Curves Using UDS3-EF/vWMH




*n*=335

Diagnostic accuracy of PlGF is retained using continuous clinical (UDS3) and radiographic (vWMH) measures:

- CSVD only = 0.73
- VCI = 0.78
- VD = 0.85
- Non-vasc CID = 0.61 (n.s.)

**Hinman et al. *Alz & Dement 2023***

# Ongoing NIH initiatives for VCID


Analyze, optimize, and validate VCID biomarkers


Mechanisms of Post-stroke VCID


White Matter Lesions in Diverse Individuals Across the U.S.

# The Challenge of Biomarker Choice for VCID

- ”Type” of VCID – small / large vessel, ischemic / hemorrhagic, inflammatory?
- “Progression” – varying rates of progression make clinical trial endpoints particularly challenging.
- 
- “Diagnostic” vs “stratification” vs “target engagement” biomarkers will likely be very different.

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SCHOOL OF MEDICINE

# Acknowledgements


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Brian Gold PhD
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Gregory Jicha MD PhD
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## MarkVCID Colleagues

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