NINDS Programs and Vision for the Science of Vascular Contributions to Cognitive Impairment and Dementia (VCID)

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National Institute of Neurological Disorders and Stroke (NINDS)
National Institutes of Health (NIH)

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Addressing AD/ADRD is a National Priority
Congress Has Chosen to Act

- ❑ Irreversible, progressive brain diseases that affect more than 5.8 million people in U.S.
- ❑ Slowly destroy brain function leading to cognitive decline, behavioral and psychiatric disorders, declines in activities of daily living and self-care
- ❑ Major public health issue affecting health and finances individuals, families, and the overall population
- ❑ **Initially named disorders: AD, FTD, LBD, MED and vascular dementia – what is vascular dementia, what is included, actually?**

The NAPA law (2011) offers a historic opportunity to address AD/ADRD

Goal 1 of the National Plan is to Prevent or Treat AD/ADRD by 2025

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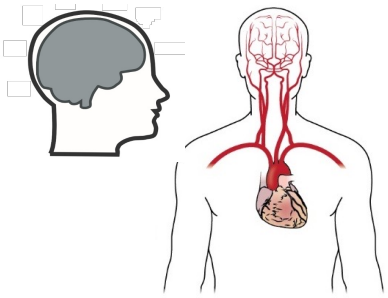
Vascular Dementia Has Been A Challenge
Vascular Cognitive Impairment Has Been A Challenge

- Science in early stages and complex
- Modest scale research relative to disease burden
- Clinically oriented but often ambiguously tied to specific diagnoses, with definitions and use that vary by region, practice, individuals, and over time
- Research & researchers isolated, fragmented across traditional fields, e.g., stroke versus dementia
- Lack of recognition of a field; lack of agreement of what that field would be

Potential lost opportunity under National Plan



Vascular Cognitive Impairment
Vascular Dementia
Vascular Brain Injury
Multi-Infarct Dementia
Post-Stroke Dementia
Etc. Etc. Etc.

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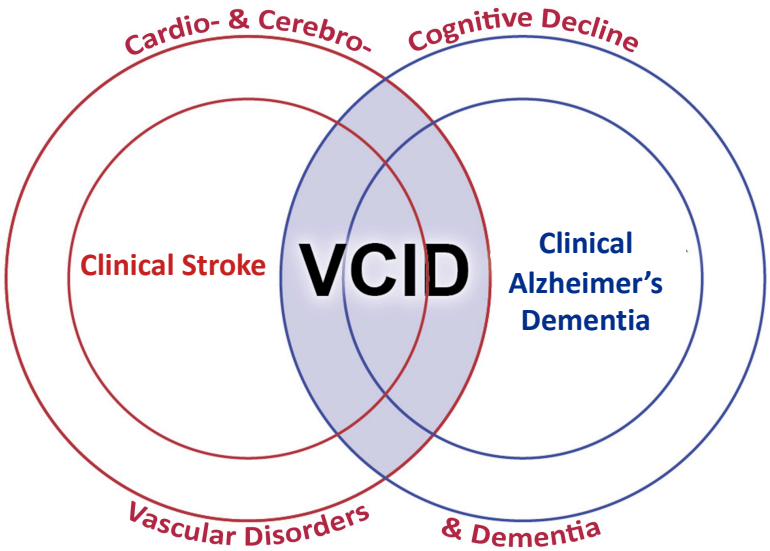
The Science of VCID Overlays Clinical Syndromes



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Therefore, NINDS Proposed in 2014:

Vascular Contributions to Cognitive Impairment and Dementia (VCID)

Field of research investigating hypothesis that significant AD/ADRD disease burden due to cognitive decline results from damage to brain function due to vascular insults of any type

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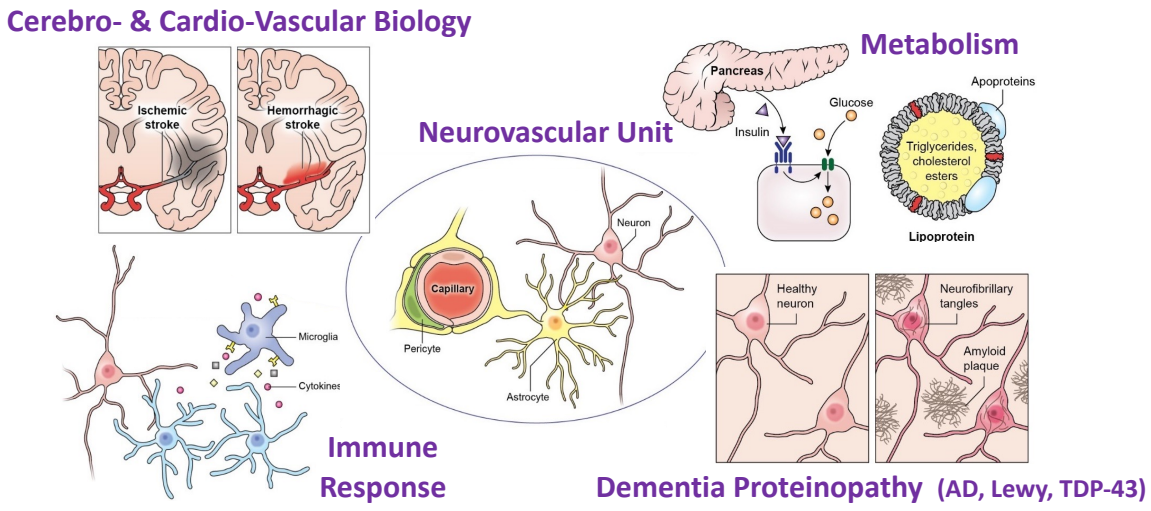
The Science of VCID is Interdisciplinary



Mechanism-oriented VCID research is best described as the neurovascular unit integrating, and failing to cope with, biological insults due to cerebro- & cardio-vascular disease, proteinopathy, metabolic disease, & immune response.

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NIH ADRD Summits Shape ADRD Research Priorities

NAPA Goal 1: Prevent and Effectively Treat AD/ADRD by 2025

Triennial AD, ADRD & Care Summits → Research Recommendations → Milestones → Scientific Advances Toward Goal 1

ADRD Summits: 2013, 2016, 2019, 2022

- ❑ **NIA leads NIH response to the National Plan* to Address AD/ADRD**
- ❑ **NINDS leads LBD, FTD, VCID & the ADRD Summits**
- ❑ **NINDS and NIA collaborate closely**
  - ➢ Funding opportunities
  - ➢ Supplement program to expand the field
  - ➢ Paylines
  - ➢ Triennial Summits

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*https://aspe.hhs.gov/reports/national-plan-2021-update

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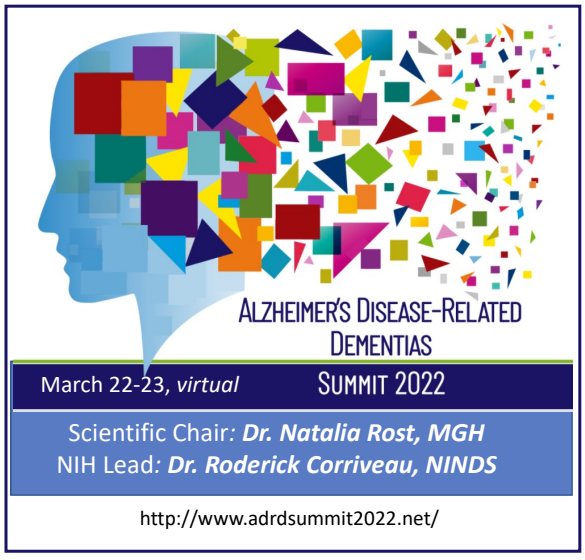
NIH ADRD Summits Shape ADRD Research Priorities



Summit Topics

- ❑ Health Equity in AD/ADRD
- ❑ Frontotemporal Degeneration (FTD)
- ❑ Vascular Contributions to Cognitive Impairment and Dementia
- ❑ Lewy Body Dementias (LBD)
- ❑ Multiple Etiology Dementias (MED)
  - ▪ Post-TBI AD/ADRD
  - ▪ LATE (TDP-43 Pathology in Common, Late-Onset Dementias)
  - ▪ COVID-19 and AD/ADRD

Planning Efforts

- ✓ Develop draft research milestones via a think tank process with broad stakeholder input
- ✓ Present draft milestones at the Summit for open forum discussion and further public input
- ✓ Finalized milestones to DHHS for the National Plan
- ✓ Inform AD Bypass Budgets delivered by NIH to Congress

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Pathway to Dementia

Alzheimer's Disease

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Multiple Potential Pathways to Dementia

LIFESTYLE FACTORS
- Physical Activity
- Diet
- Drug/Alcohol Abuse

ENVIRONMENTAL FACTORS
- Education
- Brain Trauma
- Toxins/Other

PSYCHOSOCIAL FACTORS
- Depression/Anxiety

OTHER MEDICAL RISKS
- Metabolic / Obesity / Diabetes
- Hypertension / Heart Disease / Stroke
- Inflammation
- Certain Infectious Diseases
- Certain Medications

HEALTH EQUITY FACTORS

AGING

GENETIC

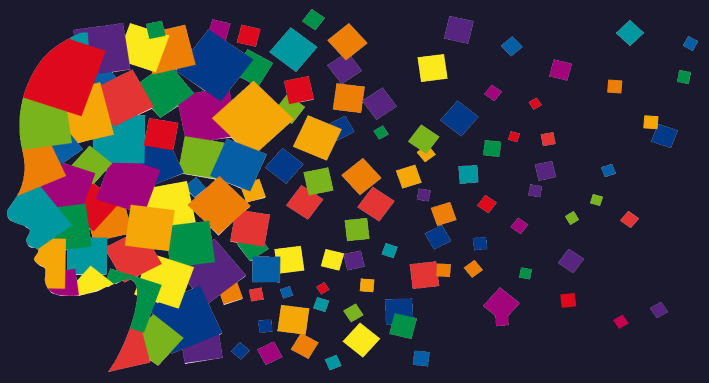
FACTORS

SEX F>M

***MISFOLDED PROTEINS**
- Amyloid
- Tau
- Alpha Synuclein
- TDP-43

***VASCULAR DISORDERS**
- Injury, Infarct (Stroke)
- White Matter Disease
- Other Vessel Disease

***OTHER DISORDERS**



COGNITIVE IMPAIRMENT and DEMENTIA DIAGNOSES

Alzheimer's Dementia	Limbic Predominant TDP
Lewy Body Dementias	Mixed Dementias
Vascular Dementias	Other Cognitive Impairment
Frontotemporal Dementias	Other Dementias

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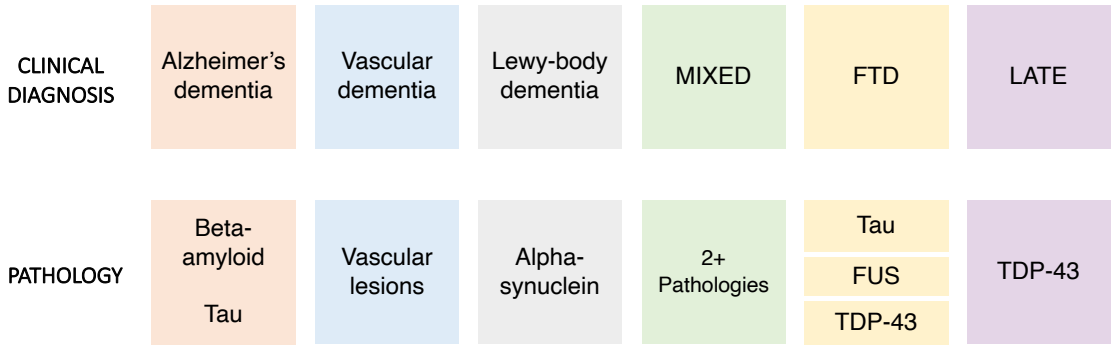
Common Perception Regarding Relationship Between Brain Pathologies and Clinical Dementia Diagnoses



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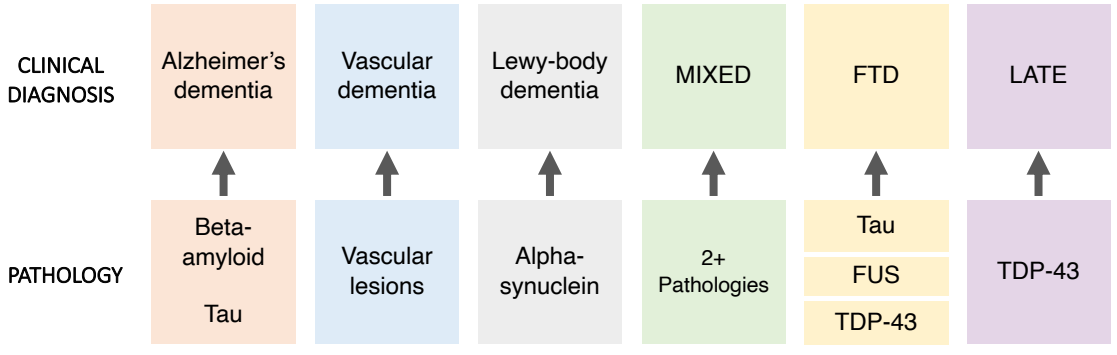
Traditional Perception of Relationship Between Brain Pathologies and Clinical Dementia Diagnoses

In terms of overall disease burden this is the exception, not the rule



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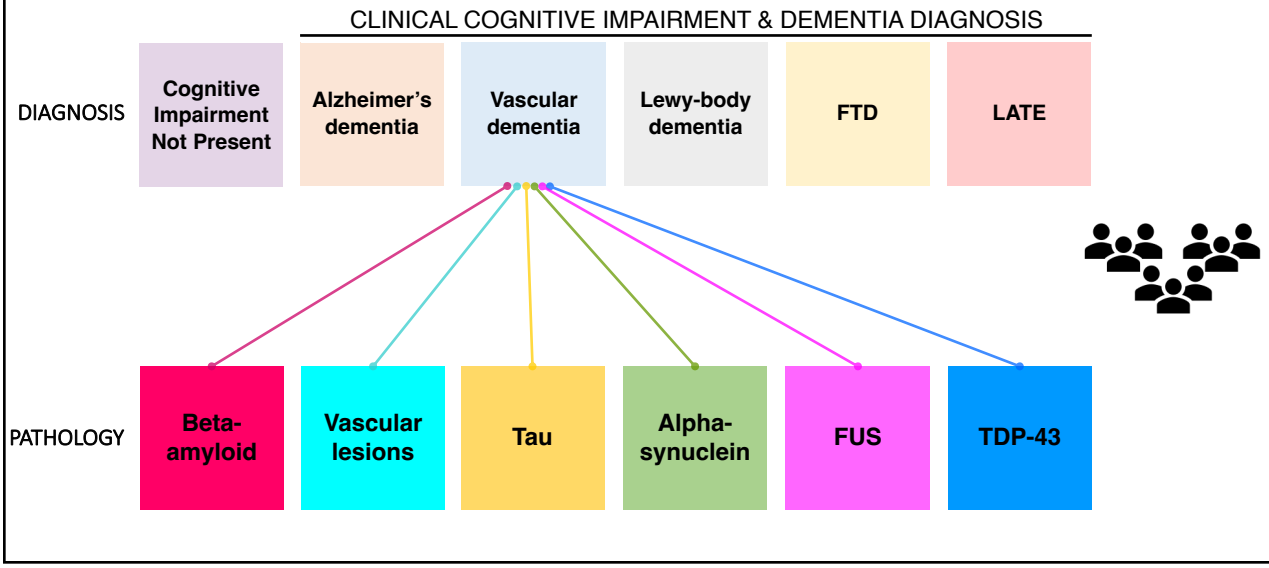
Increased Recognition That More Than One Disease Process is Typically Present in a Person's Brain Will help Move Field Move Closer to Effective Treatments



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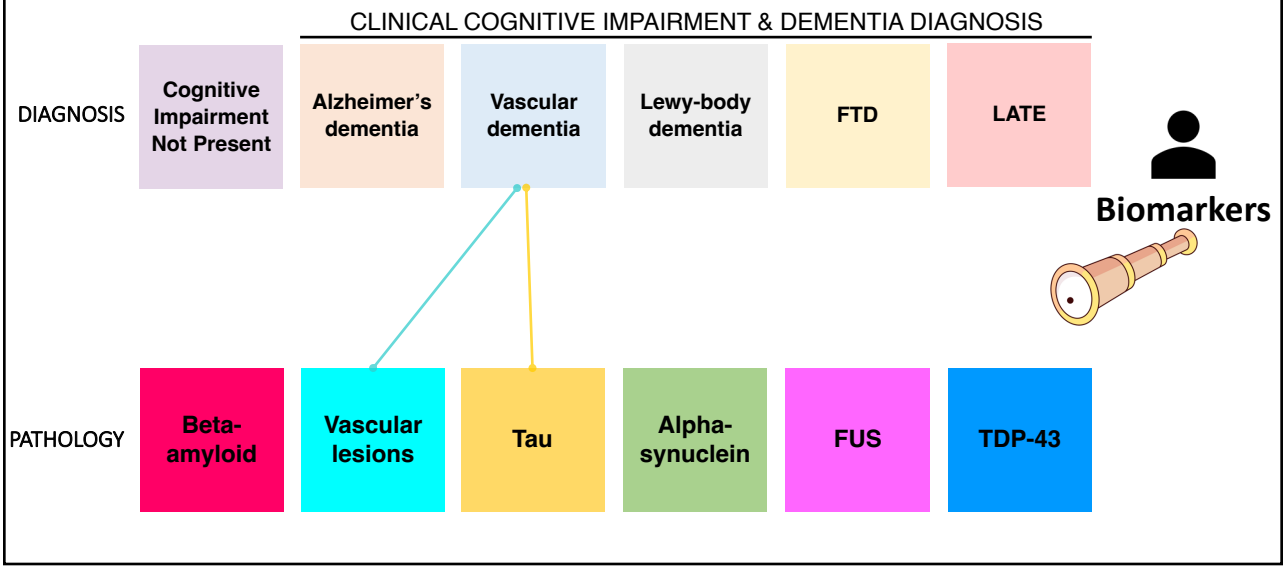

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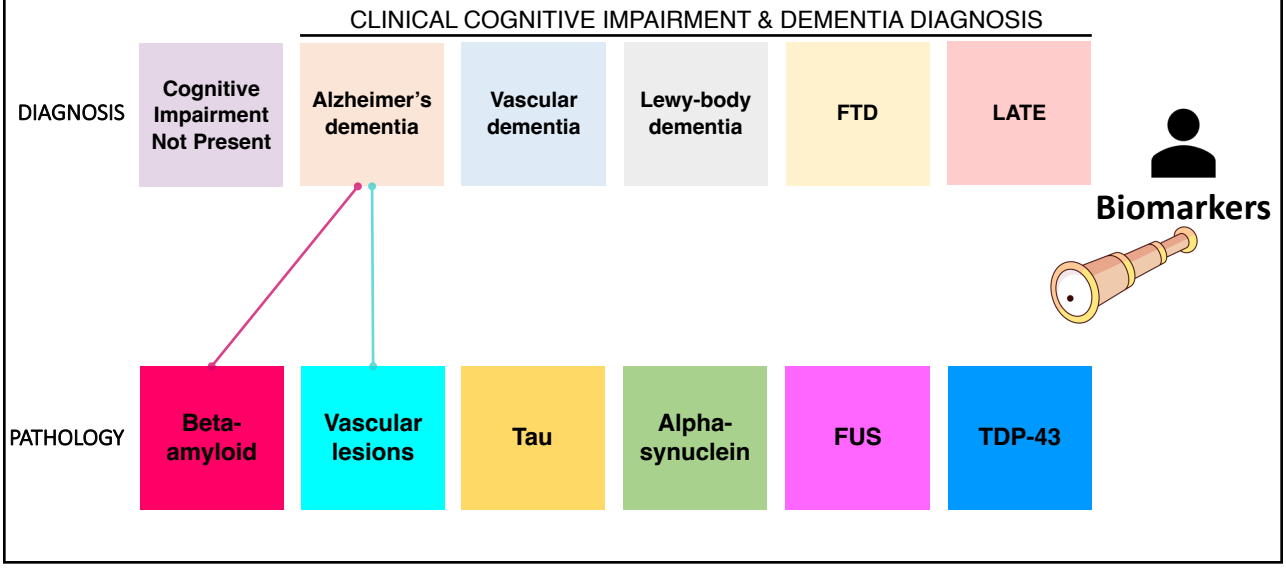

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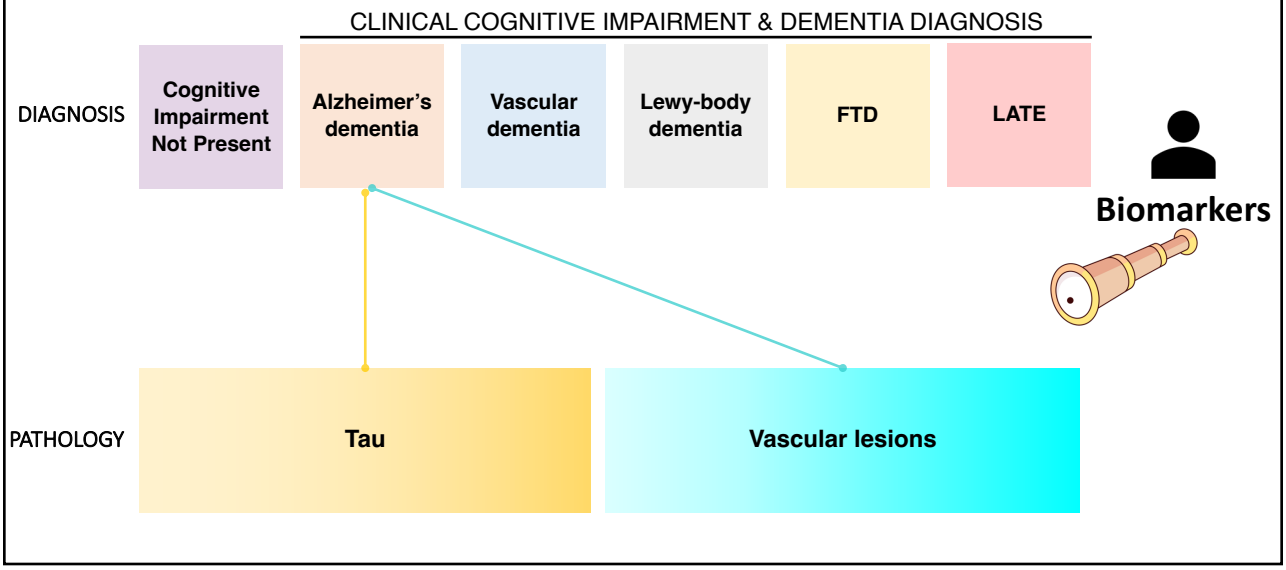

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ALZHEIMER'S DISEASE-RELATED DEMENTIAS SUMMIT 2022

Vascular Contributions to Cognitive Impairment and Dementia

Draft Recommendations

Focus Area 1: ***Basic Mechanisms and Experimental Models***	**Recommendation 1 – Priority 1.** Establish and refine **experimental models and technologies** to identify disease-relevant mechanisms underlying VCID (5-8 yrs). **Recommendation 2 – Priority 3.** Study the **neurovascular unit structure and function** to establish how it is impacted by VCID (4-6 yrs). **Recommendation 3 – Priority 4.** Use experimental models to **investigate how aging, cerebrovascular and cardiovascular disease impact myelin, white matter degeneration and neurodegeneration** (5-8 yrs).
Focus Area 2: ***Human Studies***	**Recommendation 4 – Priority 1.** Develop and validate **markers of VCID** in diverse populations using 1) cognitive, physical, or other **functional assessments**, and 2) **biomarkers** of key vascular processes, including in the most common scenario where VCID is accompanied by AD in human studies (3-5 yrs). **Recommendation 5 – Priority 2.** Identify and apply 1) **interventions** (medication, lifestyle or a combination of these) that reduce cardiovascular and cerebrovascular risk and 2) **care models** to test their efficacy for prevention and treatment of VCID across the spectrum of severity and in diverse populations (7-10 yrs). **Recommendation 6 – Priority 4.** Understand the **impact on VCID of other known dementia risk factors** (e.g. aging, genetics) and co-morbid neurodegeneration along the life-course in diverse populations (7-10 yrs).
Focus Area 3: ***Translational Studies***	**Recommendation 7 – Priority 2**. Incorporate VCID **mechanisms** derived from basic science animal/human studies into the design of human trials targeting prevention or treatment of dementia/mild cognitive impairment (5-7 yrs). **Recommendation 8 – Priority 3**. **Validate hypothesized mechanisms** of VCID in large-scale, including community-based diverse, **human studies** leveraging existing and in-process biospecimens, genomics, and imaging data (4-6 yrs).

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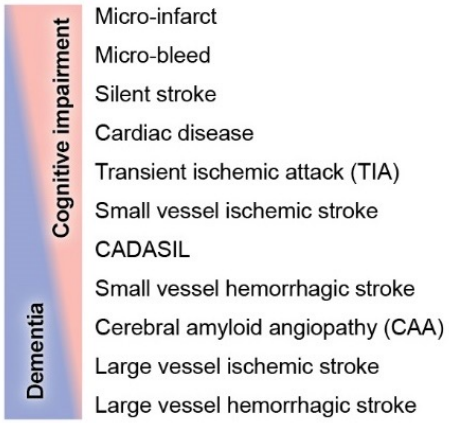
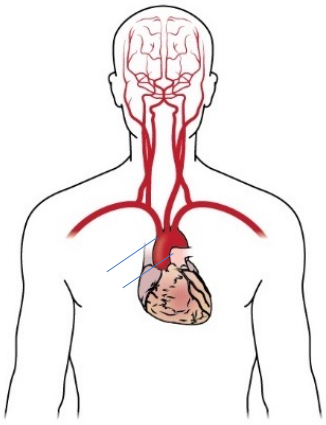
VCID Reflects Varied Vascular Injuries and Disease, Thus, Numerous Potential Mechanisms





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** ✓ **Interventions**

✓ **Biomarkers** ✓ **Clinical Trials**

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NIH Funding for AD/ADRD Research (in Millions)

Fiscal Year:	2015	2016	2017	2018	2019	2020	2021	*2022* estimated*	**Difference** 2015 to 2021
AD/ADRD[1]	**$631**	**$986**	**$1,423**	**$1,911**	**$2,398**	**$2,869**	**$3,251**	*$3,553*	**5.2-fold**
Alzheimer's Disease (AD)	**$589**	**$929**	**$1,361**	**$1,789**	**$2,240**	**$2,683**	**$3,059**	*$3,348*	**5.2-fold**
ADRD[1]	**$120**	**$175**	**$249**	**$387**	**$515**	**$600**	**$725**	*$788*	**6.0-fold**
Frontotemporal Dementia (FTD)	**$36**	**$65**	**$91**	**$94**	**$158**	**$166**	**$164**	*$169*	**4.6-fold**
Lewy Body Dementia (LBD)	**$15**	**$22**	**$31**	**$38**	**$66**	**$84**	**$113**	*$123*	**7.5-fold**
Vascular Contributions to Cognitive Impairment and Dementia (VCID)	**$72**	**$89**	**$130**	**$259**	**$299**	**$362**	**$455**	*$493*	**6.3-fold**

Spending Categories From NIH's Research, Condition, and Disease Categories (RCDC) System
Source: https://report.nih.gov/categorical_spending.aspx

1 - The Alzheimer's Disease Related Dementias (ADRD) category reflects the sum of the three existing categories: Frontotemporal Dementia, Lewy Body Dementia and Vascular Cognitive Impairment/Dementia – where duplicates are removed. Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD) reflects the sum of the two existing RCDC categories: Alzheimer's Disease (AD) and the above Alzheimer's Disease Related Dementias (ADRD) – where duplicates are removed.

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NINDS VCID Research Program – Summary

- ❑ **NINDS ADRD Summits set National Research Priorities (2013, 2016, 2019, 2022)**
  - ➢ 55 ADRD FACA-approved research milestones in National Plan
    - ➢ 8 VCID FACA-approved research milestones in HHS National Plan
- ❑ **65 NINDS ADRD funding initiatives** (18 VCID focused, plus cross-cutting)
- ❑ **11 major ADRD programs and consortia** (3 VCID specific)
- ❑ **NIH ADRD research funding increased 6-fold 2015 - 2021 ($725 M)**
  - ➢ VCID research funding increased 6.3-fold 2015-2021 ($455 M)
- ❑ **NINDS ADRD program has guided transformative research and contributed to new advanced understanding toward interventions**

DISCOVERY Determinants of Incident Stroke Cognitive Outcomes and Vascular Effects on RecoverY

DIVERSE VCID

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Examples of Recent Major VCID Research Programs

Understanding How Stroke & Comorbidities Lead to Dementia

U19 award to determine specific subsets of incident stroke that cause cognitive impairment and dementia in post-stroke populations, including in health disparities populations, & what additional clinical factors and comorbidities may causally synergize with stroke to result in cognitive impairment and dementia outcomes

DISCOVERY
Determinants of Incident Stroke Cognitive Outcomes and Vascular Effects on RecoverY

Clinical Significance of White Matter Lesions in Dementia

U19 to Examine Clinical Significance of Incidental White Matter Lesions

- Large, prospective study enrolling a diverse population with cognitive complaints
- In-depth MRI characterization of WML volume and anatomical features
- Ultimate goal is to build and validate a predictive risk model for cognitive decline

DIVERSE

Development and Validation of Biomarkers for VCID

UH2/UH3/U24 (initial stage, Y1-5) & U01/U24 (stage 2, Y6-10) awards to create a national consortium with scientific and experimental infrastructure to develop and validate predictive, diagnostic, target engagement and progression biomarkers for VCID

- Multi-site clinical testing
- Appropriately powered for completion of longitudinal validation of VCID biomarkers for use in clinical trails, including in diverse populations

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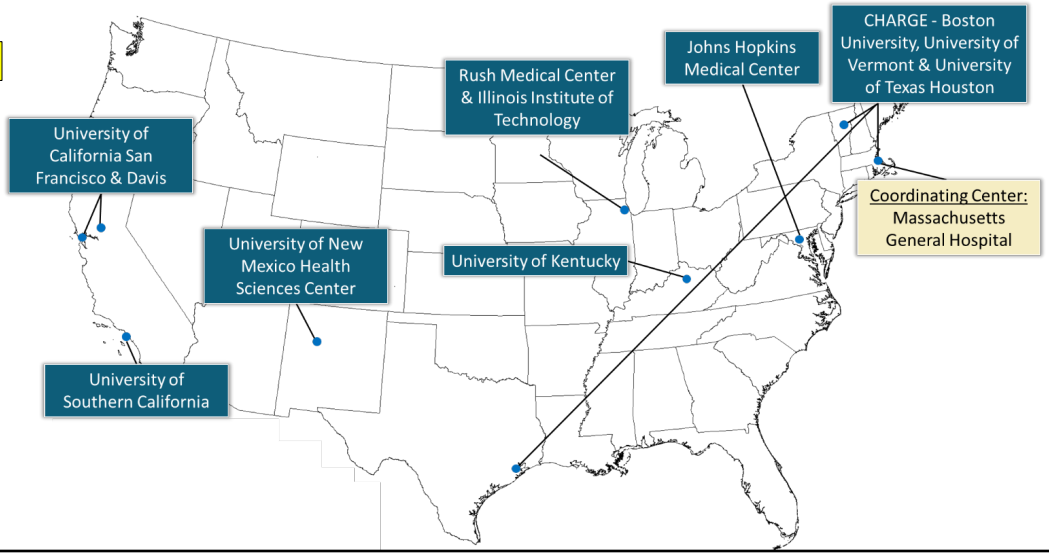
Mark VCID

National consortium to develop and validate biomarkers for small vessel human VCID including in clinical Alzheimer's and other mixed dementias.

First phase



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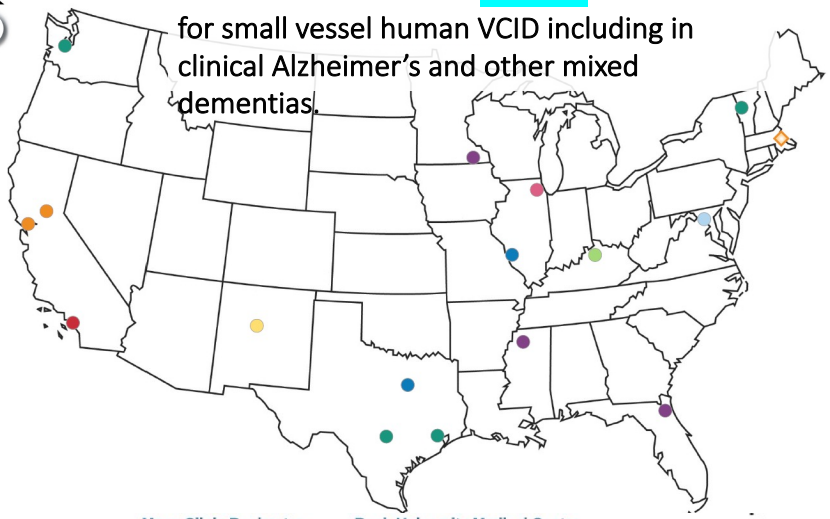
National consortium to validate biomarkers for small vessel human VCID including in clinical Alzheimer's and other mixed dementias.

Second phase



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Los Angeles & Davis

University of New Mexico Health Sciences Center

Mayo Clinic Rochester
Mayo Clinic Florida
University of Mississippi

Rush University Medical Center
Illinois Institute of Technology
University of Illinois Chicago

University of Kentucky

University of Southern California
UCLA

Washington University St. Louis
University of Texas, Southwestern

Johns Hopkins University

University of Texas Health San Antonio
UT Houston
University of Vermont

Mass General Brigham Coordinating Center

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MarkVCID Biomarker Selection: Six Year Collaboration and Process

MarkVCID Y1-Y2: Start = 9/2016

Proposed (47)

- Feasibility
- Building consortium
- Standardized, optimized protocols; core clinical data
- Sharing agreements

- Input from Coordinating Center, reviewed by EAC.

MarkVCID Y3 –Y5

Multi-Site Feasibility Testing (11)

- NINDS decisions directly reflect CC input and EAC review.
- Susceptibility/risk (8), diagnosis/subtype (2), & disease progression (1)

MarkVCID 2

Clinical Validation (5)

- NINDS decisions based on EAC input
- All 5 proposed as susceptibility/risk biomarkers as defined by the FDA:

1. Arteriolosclerosis (ARTS)
2. Cerebrovascular Reactivity
3. MRI Free Water
4. Neurofilament Light (NfL)
5. Peak Skeletonized Mean Diffusivity

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

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VCID NINDS Funding Opportunity Announcements 2016-2021

RFA-NS-16-021	**Mechanistic Basis of Diffuse White Matter Disease in Vascular Contributions to Cognitive Impairment and Dementia (VCID) (R01).** (Reissued as PAR-18-413 and RFA-NS-19-039). 3 Awards, 4 publications	Mechanism
RFA-NS-16-019 RFA-NS-16-020	**Vascular Contributions to Cognitive Impairment and Dementia (VCID) Biomarkers Consortium: Coordinating Center (CC) (U24) & Biomarkers Development Projects (Sites) (UH2/UH3).** 1 Award (CC), 7 Awards (sites), "MarkVCID": 11 VCID biomarker kits that have been instrumentally validated	Biomarker Clinical
PAR-18-413	**Mechanistic Basis of Diffuse White Matter Disease and Small Vessel Pathology in Vascular Contributions to Cognitive Impairment and Dementia (VCID) (R01).** 8 Awards	Mechanism
RFA-NS-19-012	**Post-Stroke Vascular Contributions to Cognitive Impairment and Dementia (VCID) in the United States Including in Health Disparities Populations (U19).** 1 Award	Mechanism
RFA-NS-19-039	**Mechanistic Basis of Diffuse White Matter Disease in VCID (R01).** 1 Award	Mechanism
RFA-NS-20-004	**Molecular Mechanisms of Blood-Brain Barrier Function and Dysfunction in Alzheimer's Disease and Alzheimer's Related Dementias (R01).** 4 Awards	Mechanism
RFA-NS-20-013	**White Matter Lesion Etiology of Dementia in the U.S. Including in Health Disparity Populations (U19).** 1 Award, "DiverseCID"	Biomarker Clinical
RFA-NS-20-012	**Clinical Trials Planning for Symptomatic Vascular Contributions to Cognitive Impairment and Dementia (VCID) (R34).** No awards	Clinical
RFA-NS-21-004 RFA-NS-21-005 RFA-NS-22-017	**Small Vessel VCID Biomarkers Validation Consortium Coordinating Center (U24) & Validation Consortium Sites (U01).** 9 sites, 1 Coordinating Center	Biomarker Clinical
NOT-NS-21-038	**Notice of Special Interest: Hyperacute MRI Imaging Studies to Understand How Brain Changes Affect AD/ADRD-Relevant Trajectories and Outcomes Post-Stroke (Admin Supplement).** 1 Award	Translational Mechanism
NOT-NS-21-039	**Notice of Special Interest: Innovative Approaches or Technologies to Investigate Regional, Structural and Functional Heterogeneity of CNS Small Blood and Lymphatic Vessels in AD/ADRD (Admin Supplement).** 4 Awards	Mechanism

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VCID NINDS Funding Opportunity Announcements Since 2022

PAR-22-026	**Selectively Target Technology Development to Understand How Changes or Dysfunction at the Capillary, Arterioles, and Small Lymphatic Vessels Level Can Have Long-term Impact on AD/ADRD (R01).** (closed)	Mechanism
PAR-22-037	**Role of Astrocytes in Degeneration of the Neurovascular Unit in AD/ADRDs (R01).** (closed)	Mechanism
NOT-NS-22-001	**Postmortem Pathology, Cellular, and Molecular Analyses to Determine the Significance of White Matter Lesions and other Imaging Findings of Presumed Vascular Origin During Life (admin supplement).** (closed)	Mechanism Biomarker Clinical
RFA-NS-23-001	**Pragmatic Clinical Trials in Community Settings to Decrease or Prevent VCID Outcomes, Including in Populations that Experience Health Disparities (U01 Clinical Trial Required).** (Due date September 15, 2022)	Clinical

- ❑ **14 NINDS ADRD funding initiatives are planned for FY 2023, for more information see:** https://www.ninds.nih.gov/Current-Research/Focus-Disorders/Alzheimers-Related-Dementias
- ❑ **No RFA/PAR is needed to apply!! NINDS special AD/ADRD payline for investigator-initiated research applications to NIH Parent R01 and NINDS R21 (PA-21-219)**

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NINDS ADRD Programs Address Health Equity

detectCID

Leading the effort to improve the quality of patient evaluations for detecting cognitive impairment in everyday clinical settings

- Includes a strong focus on populations that experience health disparities

VCID and Stroke in a Bi-racial National Cohort

REGARDS = REasons for Geographic and Racial Differences in Stroke

- Epidemiologic/prospective study of stroke risk in diverse populations since ~1980
- REGARDS has shifted its focus to "VCID and Stroke in a Bi-racial National Cohort"

REGARDS – Reasons for Geographic and Racial Differences in Stroke

AD/ADRD Research Supplements to Promote Diversity in Health-Related Research NOT-NS-21-047

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NIH Mind Your Risks®

https://youtu.be/gte5j2S0RuY

https://www.mindyourrisks.nih.gov/

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NINDS AD/ADRD Program - Thank You to NINDS staff, NIA Partnership & NIH Leadership

NINDS AD/ADRD Virtual Office

Rod Corriveau: Program Lead
Kiara Bates: Program Specialist
Erin Bryant: ONCE
Roger Campbell: FMB
Chi Chang: FMB
Sara Dodson: Policy Office
Amber McCartney: HPS
Nia Pree: GMB
Arvind Shukla: HPS
Keith Whitaker: Project Manager

NINDS AD/ADRD SRB

Karrah Benson
Bo-Shiun Chen
Gary Marlowe
Marilyn Moore-Hoone

NINDS AD/ADRD Portfolios

AD, MED: Linda McGavern
FTD: Tom Cheever
LBD: Deb Babcock
Tom Cheever
Beth-Anne Sieber
VCID: Rod Corriveau

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Thank you

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