National Institute of Neurological Disorders and Stroke

NINDS Role in AD/ADRD Research

October 19, 2018

Roderick Corriveau, PhD
Program Director &
AD/ADRD Program Lead, NINDS

The National Alzheimer's Project Act & the Role of NINDS

- NAPA defines **"Alzheimer's"** as **"Alzheimer's disease and related dementias"**
- **The National Plan** includes **annual recommendations for priority actions to** improve health outcomes for individuals with AD/ADRD, including via research

- The NINDS and NIA Collaborate on AD/ADRD Research
  - ***NIA is the NIH lead for AD research and responding to the National Plan***
  - ***NINDS is the NIH lead for ADRD research, including ADRD Summit planning***

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

Triennial ADRD Summits → **Research Recommendations** → **Milestones** → **Scientific Advances Toward Goal 1**

Alzheimer's Disease-Related Dementias (ADRD)

ADRD: Types of dementias that share cognitive and pathological features with Alzheimer's and/or commonly co-occur with typical Alzheimer's pathology

Vascular Dementias

- Frequently a part of typical clinical Alzheimer's disease
- Diverse spectrum of disorders **caused by cerebro- and cardio-vascular disease**
- **Reducing vascular risk factors** may decrease dementia risk

Lewy Body Dementia (LBD)

- Lewy bodies, **pathological hallmark of Parkinson's disease**, also present in brains of people with Dementia with Lewy Bodies and Parkinson's disease dementia
- Dementia occurs with problems with **movement, sleep, mood, & hallucinations**

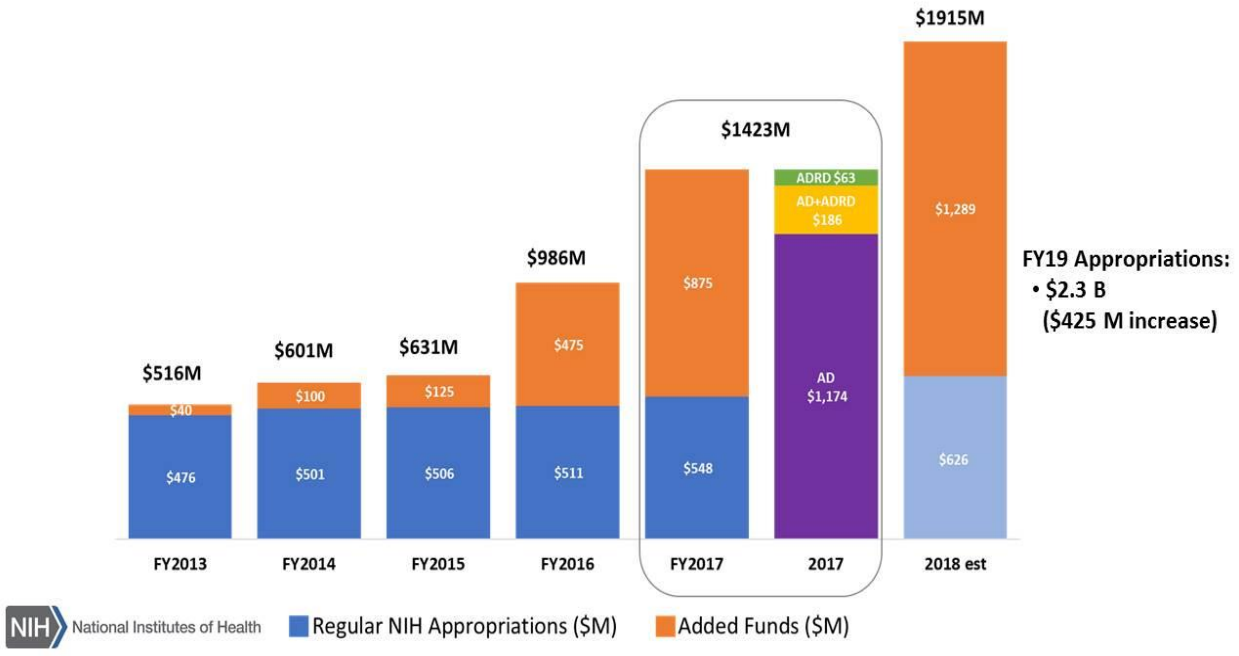
Fronto-temporal Degeneration (FTD)

- Onset often occurs **in a person's 50s or 60s**
- Progressive decline in **social behavior and/or language** (memory can be spared)
- Can be associated with **amyotrophic lateral sclerosis (ALS)**

Mixed Dementias (MED)

- Majority of all dementia cases (age 65+) are **mixed dementias**, mainly Alzheimer's pathology mixed with cerebrovascular disease and/or Lewy bodies

AD/ADRD Research Funding Increases at NIH



NIH Investment in AD/ADRD Research (millions)

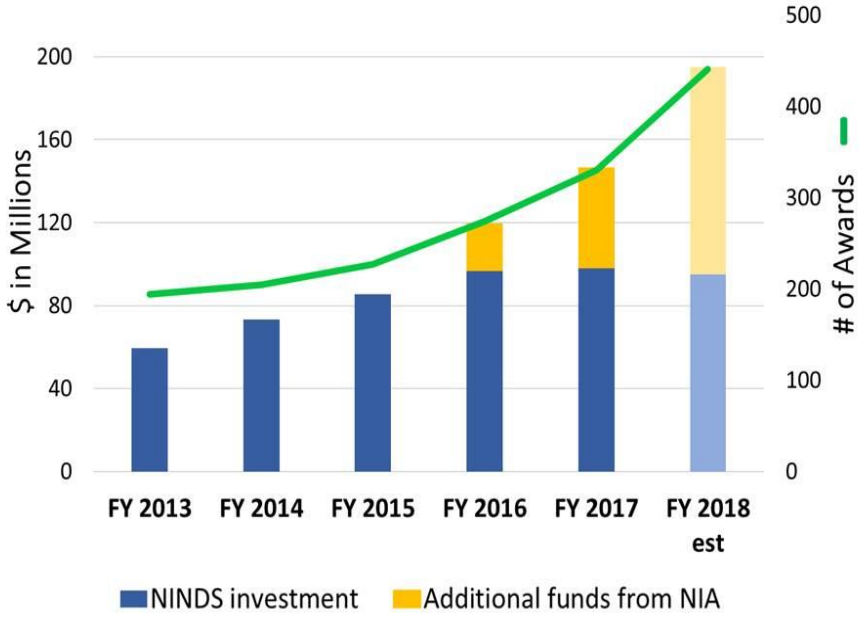
Fiscal Year:	2013	2014	2015	2016	2017	2018 est.
AD/ADRD	Category Not Yet Tracked	Category Not Yet Tracked	$631	$986	$1423	$1915
Alzheimer's Disease	$504	$562	$589	$929	$1361	$1849
Frontotemporal Dementia	$32	$37	$36	$65	$91	$96
Lewy Body Dementia	Category Not Yet Tracked	$15	$15	$22	$31	$31
Vascular Cognitive Impairment & Dementia	Category Not Yet Tracked	$45	$72	$89	$130	$137

How NINDS Leverages Funds to Advance AD/ADRD Research

Additional AD/ADRD research funds from NIA are used by NINDS for:

1) New Milestone-responsive ADRD Research Programs (FY16: $18M; FY17: $26.6M)

2) Increased Investment in Investigator-Initiated AD/ADRD Research (FY16: $5.1M; FY17: $19.6M)



ADRD Research Initiatives and Programs: Multiple Etiology Dementias, Health Disparities

MED and Health Disparities

- **DetectCID – consortium to develop paradigms to increase detection of cognitive impairment/ dementia** in primary care and health disparity populations *[3 awards; $5.6M over FY17-FY18]*
- **Health Disparities and AD (R01) FOA** – NINDS participating to encourage **health disparities research in ADRD** *[2 awards; $4.6M over FY17-FY18]*
- **VCID and Stroke in a Bi-racial National Cohort (REGARDS longitudinal study)** *[FY18]*
- **Recruitment and Retention Strategy for Clinical Research Planning Efforts led by NIA**
- **Scholarship Program for ADRD Summit 2019** *[up to 15 recipients]*

Responsive to Milestones for:

Multiple Etiology Dementias

- Detect cognitive impairment when a patient, relative, or care provider voices a concern
- Improve differential diagnosis of symptomatic cognitive impairment

Health Disparities

- Assess epidemiology and mechanistic pathways of disparities in health burden of AD/ADRD
- Increase utilization of culturally and linguistically appropriate assessment tools

NINDS ADRD Research Initiatives and Programs for Lewy body Dementia

Lewy Body Dementia (LBD)

- **Supporting biomarker discovery studies for LBD** by including data and biospecimens from patients with LBD to the NINDS PDBP *[5 awards; $13.2M over FY16-FY18]*
- **Leveraging existing LBD data and biospecimens in ADNI/NACC and PDBP** for research on LBD *[2 awards; $293K over FY17-FY18]*
- **Pathway and Target Identification for LBD and AD/ADRD** genes, control regions, pathways, cell types, and brain regions *[1 awards; $1.4M in FY18]*
- **Structural Biology** of alpha-synuclein in LBD *[1 awards; $837K in FY18]*

Responsive to Milestones for:

Lewy body dementias

- Create longitudinal clinical, biological, and imaging resources to improve detection and diagnosis of DLB at the predementia or prodromal stage including patients at high risk of PD
- Characterize nervous system changes in LBD cohorts that have come to autopsy to identify disease-specific underlying mechanisms to guide biomarker and therapeutic approaches
- Identify novel common and rare genetic variants, epigenetic changes, and environmental influences that affect the risk for and clinical features of LBD

NINDS ADRD Research Initiatives and Programs for Frontotemporal Degeneration

Fronto -temporal Degeneration (FTD)

- **Multi-center, interdisciplinary "Center without Walls" (Tau CWOW)** to study molecular mechanisms of tau toxicity in FTD *[2 awards; $20.8M over FY16-FY18]*
- **FTD Sequencing Consortium** to discover FTD-causing genetic mutations *[2 awards; $4.3M over FY17-FY18]*
- **Pathway and Target Identification for FTD and AD/ADRD** genes, control regions, pathways, cell types, and brain regions *[1 awards; $1.4M in FY18]*
- **Structural Biology** of Tau and TDP-43 in FTD *[2 awards; $2.2M in FY18]*

Responsive to Milestones for:

Frontotemporal lobar degeneration

- Clarify the mechanism of tau pathogenesis and associated neurodegeneration
- Expand efforts to genotype patients with FTD and identify new genes and their functional relationship to FTLD pathogenesis
- Develop FTD biomarkers for diagnosis and disease progression

NINDS ADRD Research Initiatives and Programs for Vascular Dementias

Vascular Dementias

- **MarkVCID – Small vessel VCID Biomarkers Consortium** to develop biomarkers for cerebrovascular disease for use in clinical trials *[8 awards; $26.0M over FY16-FY18]*
- Research to better understand **the mechanistic basis of small vessel and diffuse white matter disease in VCID (R01)** *[10 awards; $27.6M over FY16-FY18]*
- **VCID and Stroke in a Bi-racial National Cohort (REGARDS longitudinal study)** *[FY18]*

Responsive to Milestones for:

VCID, including vascular cognitive impairment and vascular dementias

- Develop models that reproduce small vessel disease, are relevant to VCID and AD, address white and gray matter VCID, or include genetic and acquired VCID Verify models, including via imaging
- Develop and validate longitudinally tracked noninvasive markers of key vascular processes related to cognitive and neurologic impairment
- Determine interrelationships among aging, cerebrovascular disease, and risk factors, resilience factors, genetic variants, amyloid, tau, and neurodegeneration
- Identify lifestyle and vascular interventions to treat, prevent, or postpone VCID

NINDS AD/ADRD Research Concepts Proposed FY 2019

Vascular Dementias

- Prospective clinical research to determine the stroke and events and comorbidities that increase risk for or cause **Cognitive Impairment and Dementia in Post-Stroke Populations**

Lewy Body Dementia (LBD)

- **Progression Markers for Cognitive Impairment** in Parkinson's Disease Dementia (PDD)
- **Lewy Body Dementia Center without Walls** to systematically and comprehensively characterize alpha-synuclein and amyloid-beta subspecies

Fronto-temporal Degeneration (FTD)

- Collaboration with the NIA for **FTD Natural History, Biomarker, and Genetics Studies**

MED & AD/ADRD Cross Cutting

- **Advanced ADRD Animal and Cellular Models**
- **PET Ligand Development** to identify ADRD proteinopathies or pathological processes
- Studies on the **Clinical Research** and **Pathological Mechanisms of AD/ADRD in CTE/TBI**
- Validate novel **ADRD Druggable Targets** for development of pharmaceutical interventions
- **AD/ADRD Training Supplements** to mentor the researchers from underrepresented groups

NINDS ADRD Research Initiatives and Programs

supported by the additional AD/ADRD funds

Tau Center without Walls

- **Investigates molecular mechanisms that contribute to abnormal, toxic forms of tau** that are found commonly in the brains of people with FTD and Alzheimer's

West cWOW | East cWOW

Tau Center Without Walls

FTD Sequencing Consortium

- **Aims to discover and validate genetic factors (e.g., gene mutations) that increase FTD risk** in active collaboration with NGOs, and researchers at NIH

NINDS ADRD Research Initiatives and Programs

supported by the additional AD/ADRD funds

The Lewy Body Dementias Biomarkers Initiative

- **Leverages the NINDS Parkinson's Disease Biomarkers Program (PDBP)** to **support biomarker discovery studies for LBD** by adding data and biospecimens from patients with LBD

DetectCID

- National consortium developing standardized paradigms that take 10 minutes or less **to detect cognitive impairment and dementia in primary care and other everyday care settings, including in health disparities populations, and provide guidance for appropriate follow-up**

Image from UAB news

NINDS ADRD Research Initiatives and Programs

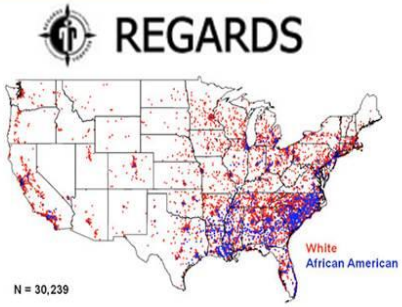
supported by the additional AD/ADRD funds

MarkVCID

- National Consortium of 7 sites and 1 coordinating center **to develop and validate biomarkers for vascular contributions to cognitive impairment and dementia (VCID)**

Reasons for Geographic and Racial Differences in Stroke

- Observational study of over 30,000 white and black Americans aged 45 or older **to improve understanding of health disparities in and relationship between vascular risk factors and dementia**

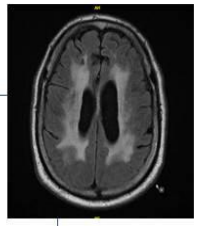


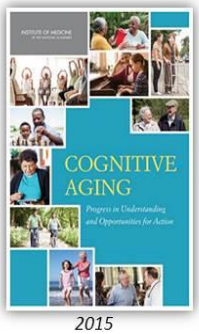
Focus on Stroke, VCID and Healthy Brain Aging

NIH National Institute of Neurological Disorders and Stroke

Director's Messages

"High blood pressure, the primary driver of stroke, is thought to impart physiological damage on blood vessels in the brain. The damage can lead to ischemic and hemorrhagic stroke and even "silent strokes" – small infarcts that go relatively unnoticed, but which affect nearly 30 percent of elderly individuals. In addition to the well-known burden of illness due to clinical stroke, decades of research has also shown a causative link between stroke and cognitive impairment and dementia late in life." "Higher blood pressure levels over time have been linked to more extensive areas of white matter damage, which itself has been linked to diminished performance on tests of cognitive function."

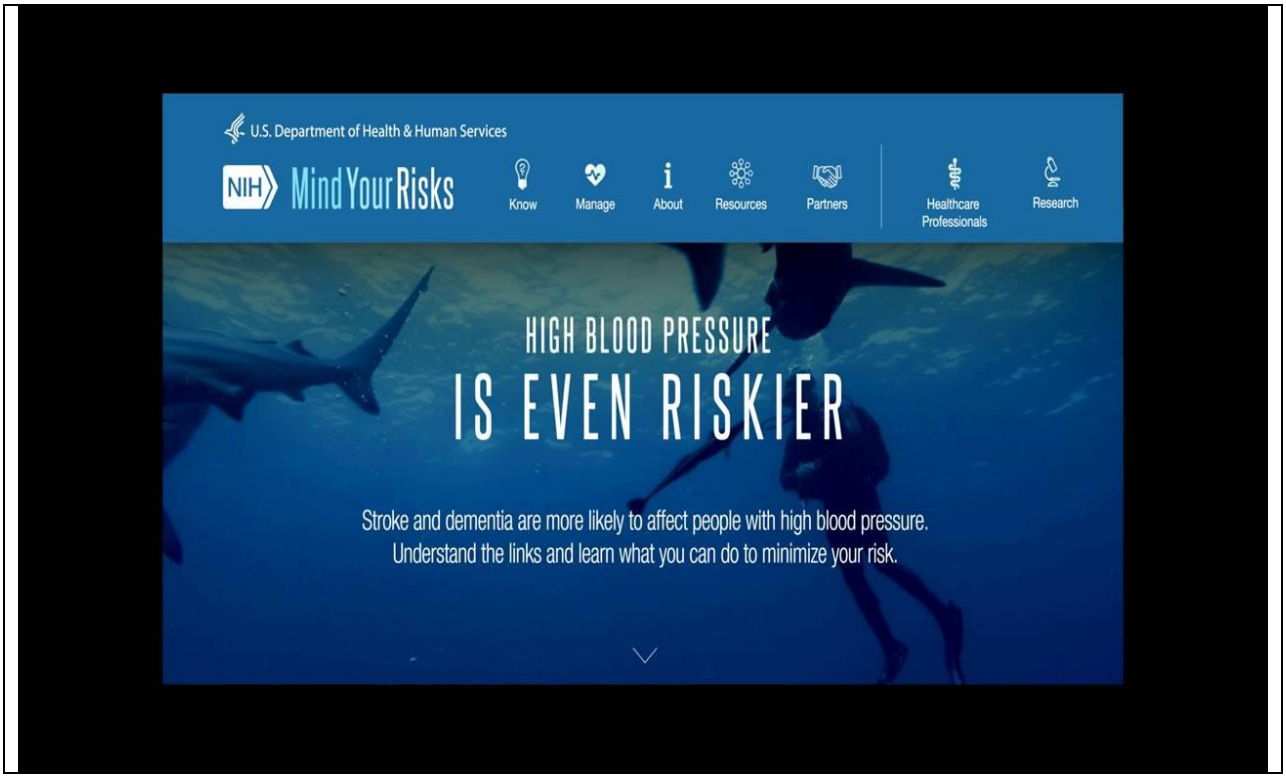




2015

Preventing Cognitive Decline and Dementia: A Way Forward (2017)
National Academy of Sciences·Engineering·Medicine
Consensus Study Report

"... some degree of support for the benefit of three classes of intervention: cognitive training, blood pressure management in people with hypertension, and increased physical activity."



Interactions with NGOs

Alzheimer's Disease-Related Dementias (ADRD) NGO Roundtable

- **June 22, 2018** at NIH
- NINDS & NIA leadership, staff, and 7 ADRD-related NGOs met to provide updates on ADRD research activities and discussed opportunities for potential collaboration

LBDA Lewy Body Dementia Association
BrightFocus® Foundation Cure in Mind. Cure in Sight.
apda American Parkinson Disease Association Strength in optimism. Hope in progress.
alzheimer's association®
AFTD The Association for Frontotemporal Degeneration FIND HELP·SHARE HOPE
American Heart Association | American Stroke Association
ALS ASSOCIATION

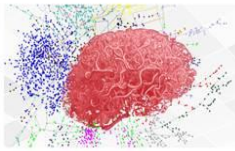
Examples of Ongoing Trans-NIH ADRD Collaborations

NINDS & **NIA** fund **ARTFL** and **LEFFTDS,** with support from **NCATS**:

- **ARTFL:** study of individuals with a clinical diagnosis of FTD to help determine clinical, genetic and biomarker profiles
- **LEFFTDS:** study of families that have one of the three most common gene variants associated with FTD to learn more about the natural history

Longitudinal Evaluation of Familial FrontoTemporal Dementia Subjects LEFFTDS

A·R·T·F·L Advancing Research & Treatment for Frontotemporal Lobar Degeneration



M²OVE-AD Molecular Mechanisms of the Vascular Etiology of Alzheimer's Disease

- 5 active awards funded by **NIA** and **NINDS**
- **M2OVE-AD** aims to gain a deeper understanding of risk phenotypes and mechanisms of VCID

NIH National Institute of Neurological Disorders and Stroke
NIH National Heart, Lung, and Blood Institute

- **VCID Workshop** (5/2018 workshop)
- **Neuropathological Impact of Sleep Deficiency & Sleep Disorders** (8/2018 workshop)
- **AD Viewed as a Neurovascular Inflammatory Disorder** (4/2017 eBriefing)

Examples of Ongoing Trans-NIH Collaborations

BASIC Project
BASIC Ancillary Sleep Study
University of Michigan

NHLBI and NINDS Funded Research into Stroke, Sleep and VCID

- Delivery of stroke care in communities
- Post-Stroke Cognitive outcomes in Mexican Americans and non-Hispanic whites

Database of research supported by public & private organizations worldwide; uses the ***C**ommon **A**lzheimer's and **R**elated **D**ementias **R**esearch **O**ntology*

IADRP
International Alzheimer's and Related Dementias Research Portfolio

Notice of Availability of Administrative Supplements for NIH Grants that are NOT Focused on Down Syndrome to Address Specific Down Syndrome Research Objectives **(NOT-OD-18-194)**

New trans-NIH program to support research on commonly co-occurring conditions in individuals with Down syndrome that are also seen in the general population, including AD/ADRD.

Examples of Trans-NIH Collaborations: Leveraging Cohorts to Address the Science of VCID

Multi-IC team (NINDS, NIA, NHLBI, NIDDK) that resulted in funding opportunities on:

- Clarifying risk and protective factors
- Harmonization of outcome measures

NINDS Support for Cohort Ancillary Studies:

- Framingham – NS017950; Precursors of Stroke Incidence and Prognosis
- Framingham, Rotterdam, ARIC, CHS cohorts – NS97541; An Integrated Genetic and Epigenetic Approach to Cerebral Small Vessel Disease

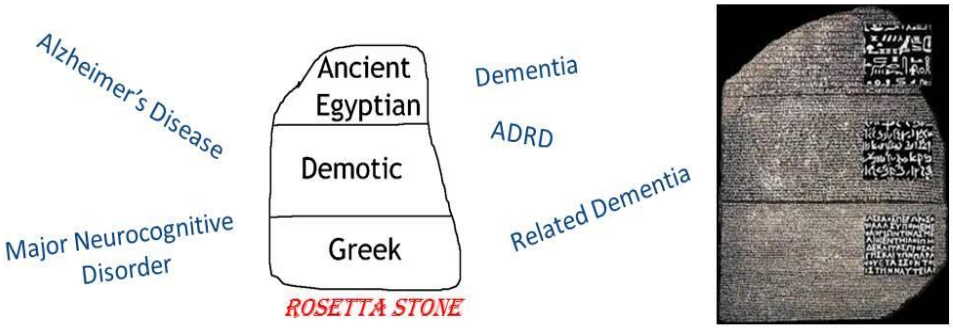
NINDS/NIA Supported Neurological and/or Cognitive Assessment for NHLBI projects:

- ARIC Neurocognitive Study (ARIC-NCS)
- Cardiovascular Health Study (CHS)
- Cardiothoracic Surgery Network
- SPRINT trial
- Hispanic Community Health Study/Study of Latinos (HCHS-SOL)

Top 30 cohorts in analysis	
ACT study [AG]	MCSA [AG]
ARIC [HL]	MESA [HL]
CARDIA [HL]	MARS [AG]
CHS [HL]	NOMAS [NS]
CIRT-MIND [HL]	REGARDS [NS]
COPDGene Study [HL]	ROS / MAP [AG]
DCCT/Epi Study [DK]	SPRINT-MIND [HL]
DPPOS [DK]	SHS [HL]
EAS [AG]	The 90+ Study [AG]
ELSA [AG]	VETSA [AG]
Framingham Cohorts [HL]	WHICAP [AG]
HRS [AG]	Whitehall II Study [AG]
HCHS / SOL [HL]	WLS [AG]
Israel Diabetes & Cognitive Decline Study [AG]	Wisconsin Sleep Study [HL/AG]
JHS [HL]	WHI cohorts [HL]

ADRD Summit 2016: Special Session

Milestone: Develop Consistent Nomenclature in Dementia Research & Care



- **Organize a working group of dementia stakeholders,** including founding partnerships with health disparities communities, **to review the current nomenclature** used in public awareness, clinical care services and research and to propose strategies to help advance early differential diagnosis and the understanding of dementia and its underlying causes

NIH National Institutes of Health

SAVE THE DATE
MARCH 14-15
2019

ALZHEIMER'S DISEASE-RELATED DEMENTIAS SUMMIT 2019:

RESEARCH CHALLENGES AND OPPORTUNITIES

MARCH 14-15, 2019
NATCHER AUDITORIUM, NIH CAMPUS, BETHESDA MD

Julie Schneider, MD
Rush University Medical Center
Scientific Chair

Roderick A. Corriveau, PhD
NINDS, Program Director
NIH Lead

Register online at:
https://meetings.ninds.nih.gov/?ID=21149

Scholarship Program: Deadline, Dec. 12

Sessions on:

- **Multiple Etiology Dementias**
- **Health Disparities**
- **Emerging Topics**
- **Nomenclature**
- **Frontotemporal Degeneration**
- **Lewy Body Dementias**
- **Vascular Contributions to Cognitive Impairment and Dementia**

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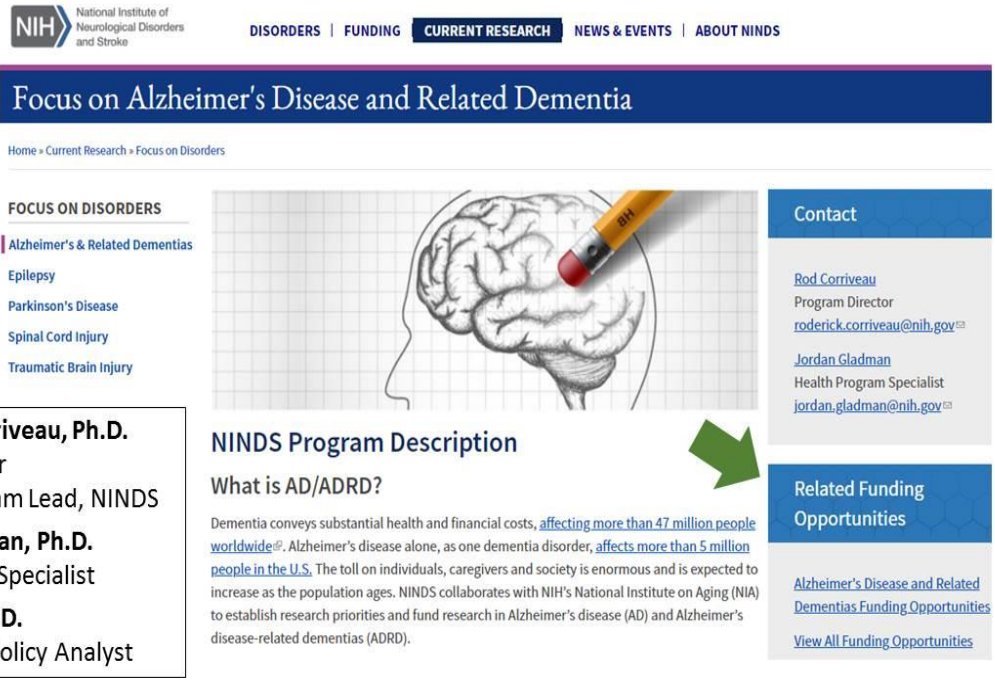
NEW NINDS AD/ADRD Web Pages:



Roderick A. Corriveau, Ph.D.
Program Director
AD/ADRD Program Lead, NINDS

Jordan T. Gladman, Ph.D.
Health Program Specialist

Sophia Jeon, Ph.D.
Health Science Policy Analyst

Thank You NIH Leadership & Colleagues

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- Francesca Bosetti
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- Robert Finkelstein
- Susan Fowler
- Jordan Gladman
- Amelie Gubitz
- Sophia Jeon
- Jim Koenig
- Christine Lam
- Timothy Lavaute
- Quynh Ly
- Ernest Lyons
- Linda McGavern
- Meghan Mott
- Claudia Moy
- Birgit Neuhuber
- David Owens
- Jonathan Sabbagh
- Joel Saydoff
- Nina Schor
- Paul Scott
- Beth-Anne Sieber
- Natalia Strunnikova
- Margaret Sutherland
- Christine Swanson-Fischer
- Amir Tamiz
- Christine Torborg
- Renee Waltzer
- Jackie Ward
- Margo Warren
- Clinton Wright

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