NIH Priorities for Alzheimer's Disease and Down Syndrome

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National Institute on Aging/National Institutes of Health
Global Down Syndrome Research and Medical Care Roundtable
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NIH National Institute on Aging

New Trans-NIH Down Syndrome Initiative

Congressional Directive for DS

- In the FY 2018 budget legislation for NIH:
  - "Develop a new trans-NIH initiative ... to study trisomy 21, with the aim of yielding scientific discoveries to improve the health and neurodevelopment of individuals with Down syndrome and typical individuals at risk for:
    - Alzheimer's disease
    - cancer
    - cardiovascular disease
    - immune system dysregulation
    - and autism,
    - among others..."

Protected from:
- Many solid tumors
- Atherosclerosis and heart attacks

- Unique double benefit: understanding both **Down syndrome** and **shared common conditions** (risks or resiliencies)

INCLUDE (**IN**vestigation of **C**o-occurring conditions across the **L**ifespan to **U**nderstand **D**own syndrom**E**)

3 Components:

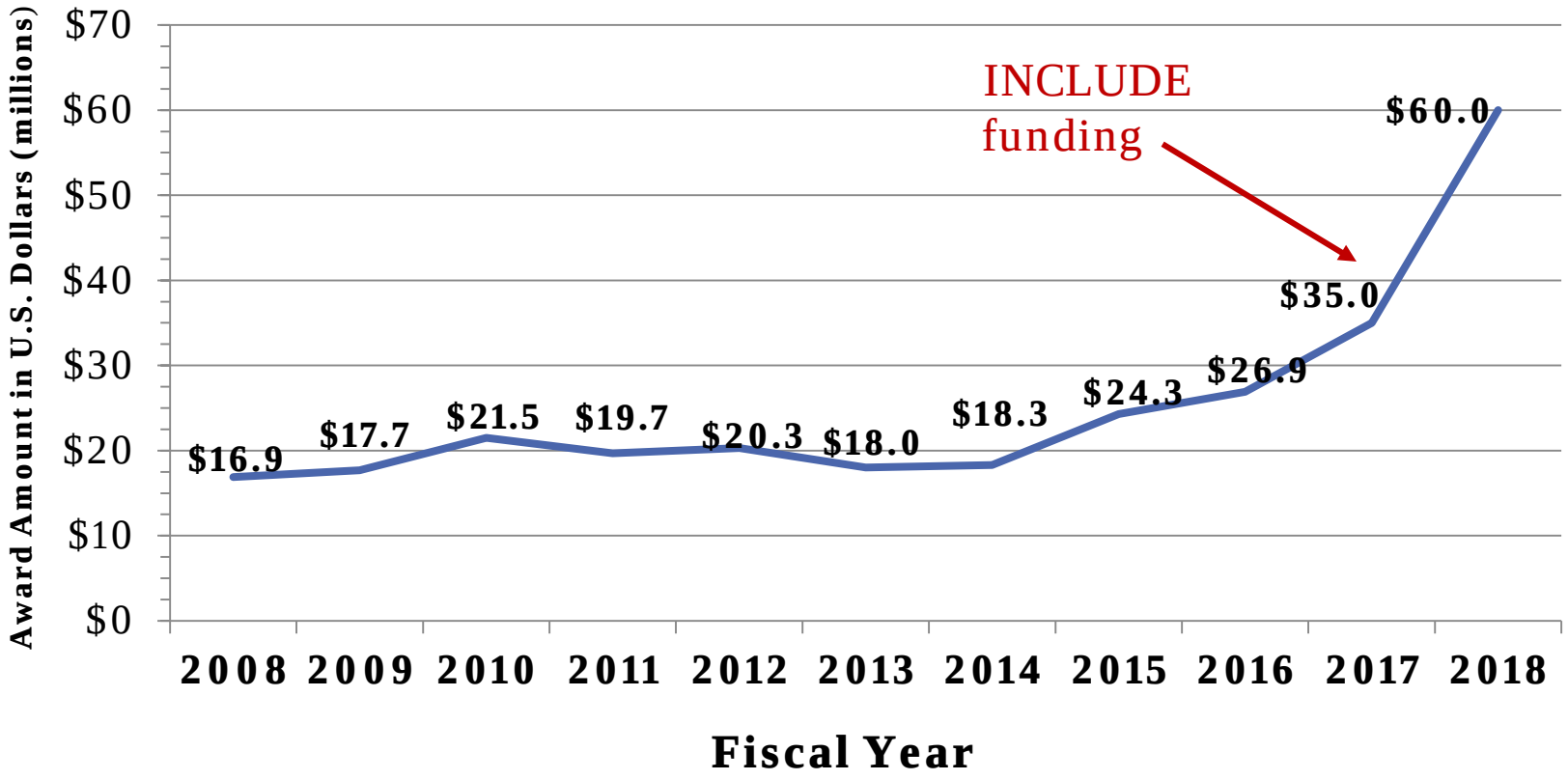
1. **Conduct targeted, high-risk, high-reward basic science studies on chromosome 21. Emphasis on studies that can inform the other two components**
2. **Assemble a large cohort of individuals with Down syndrome across the lifespan for comprehensive phenotyping and biomarker analysis.**
3. **Include individuals with Down syndrome in existing and future clinical trials.**

The INCLUDE Project: A Trans-NIH Initiative

National Cancer Institute (NCI)
National Eye Institute (NEI)
National Heart, Lung, and Blood Institute (NHLBI)
National Human Genome Research Institute (NHGRI)
National Institute on Aging (NIA)
National Institute of Allergy and Infectious Diseases (NIAID)
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
National Institute on Deafness and Other Communication Disorders (NIDCD)
National Institute of Dental and Craniofacial Research (NIDCR)
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
National Institute of Environmental Health Sciences (NIEHS)
National Institute of Mental Health (NIMH)
National Institute on Minority Health and Health Disparities (NIMHD)
National Institute of Neurological Disorders and Stroke (NINDS)
National Institute of Nursing Research (NINR)
National Center for Advancing Translational Sciences (NCATS)
National Center for Complementary and Integrative Health (NCCIH)
Office of the Director/Office of Research Infrastructure Programs (ORIP)
Office of the Director/Office of Strategic Coordination (Common Fund)

20 different NIH institutes, centers, and offices involved!

NIH Funding for Research on Down Syndrome
FY 2008 – FY 2018



FY2018 INCLUDE Funding

- **~$23 M supported 49 supplements to existing NIH grants**
- Distributed among 14 Institutes
- All 3 components addressed
- Data sharing expectation
- Leverage *DS-Connect®: The Down Syndrome Registry* when possible

https://www.nih.gov/include-project

FY2018 AD-Related INCLUDE Supplements

- Treating with gamma-secretase modulators to prevent neurodegeneration in mouse models of DS and AD – Component 1
- Enhanced metabolomics in ABC-DS (Alzheimer's Biomarkers Consortium – DS) –Component 2
- Lifestyle factors in ABC-DS – Component 2
- Role of midlife cardiovascular disease on AD pathology and cerebrovascular reactivity –Component 2
- Down Syndrome module for AD Centers (National Alzheimer's Coordinating Center -NACC) – Components 2 & 3
- Building AD-DS clinical trials infrastructure within Alzheimer's Clinical Trials Consortium (ACTC) – Component 3

Future Directions: FY2019-FY2022

- Continue support in FY2019 to fully launch the INCLUDE project
- Focus on new Requests for Applications (RFAs) to the greatest extent possible but also support additional supplements in FY2019 to further leverage existing infrastructure
- It is anticipated that this level of support will be maintained in FY2020 through FY2022
- Scientific workshops are planned for FY2019 and FY2020

FY2019 INLCUDE Funding Initiatives

Notice	INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE (INCLUDE) Clinical Trial Readiness (R21 Clinical Trial Not Allowed)
Notice Number	RFA-OD-19-015
Post Date	February 5, 2019
Expiration Date	March 15, 2019

Notice	Transformative Research Award for the INCLUDE (Investigation of Co-occurring Conditions across the Lifespan to Understand Down syndrome) Project (R01 – Clinical Trial Not Allowed)
Notice Number	RFA-OD-19-016
Post Date	February 5, 2019
Expiration Date	March 15, 2019

Notice	Clinical Trials Development for Co-Occurring Conditions in Individuals with Down syndrome: Phased Awards for INCLUDE (R61/R33 Clinical Trials Required)
Notice Number	RFA-OD-19-018
Post Date	February 5, 2019
Expiration Date	March 15, 2019

Notice	Notice of Availability of Competitive Supplements/Revisions for the INCLUDE (Investigation of Co-occurring Conditions across the Lifespan to Understand Down syndromE) Project (Competitive Supplement/Revision Clinical Trial Optional)
Notice Number	NOT-OD-19-071
Post Date	February 5, 2019
Expiration Date	See listed due dates in Notice.

Notice	Notice of Availability of Administrative Supplements for the INCLUDE (Investigation of Co-occurring Conditions across the Lifespan to Understand Down syndromE) Project (Administrative Supplement/ Clinical Trial Optional)
Notice Number	NOT-OD-19-087
Post Date	March 27, 2019
Expiration Date	May 24, 2019

Ongoing NIA/NIH Translational Initiatives and Resources for Research on Alzheimer's Disease in Down Syndrome

A Pipeline of NIA and Trans-NIH Translational Research Funding Initiatives

AMP-AD Targets
M²OVE-AD
Resilience-AD

MODEL-AD
AlzPED

ACTC
ADNI
AMP-AD Biomarkers
ABC-DS

ENABLING INFRASTRUCTURE FOR DATA DRIVEN AND PREDICTIVE DRUG DEVELOPMENT

Alzheimer's Biomarkers Consortium - Down Syndrome (ABC-DS)

Exploring the Connection Between Down Syndrome and Alzheimer's Disease

The ABC-DS study is a joint study conducted by two groups of research collaborators —Neurodegeneration in Aging Down Syndrome (NiAD) and Alzheimer's Disease in Down Syndrome (ADDS)—and is supported by the National Institute on Aging (NIA) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), both part of NIH.

https://www.nia.nih.gov/research/abc-ds

ABC-DS

- $46M consortium - Two multi-institutional, cross-disciplinary research teams (Contact PIs: NiAD - Ben Handen, ADDS - Nicole Schupf) collaborating and harmonizing measures and procedures

- Biomarkers to track AD-related changes in the brain and cognition for ~400 adults with Down syndrome (25-85 years old)

- Measures include PET (Amyloid and Tau), MRI, CSF and blood markers, DNA for GWAS, cognitive/memory tests

- Data will be available in a public database via LONI/ATRI, pre-publication; samples will be made available to qualified investigators via the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD)

ABC-DS Deliverables

- Develop valid assessment procedures for tracking clinical progression
- Determine proteomic, metabolomic and CSF biomarker profiles associated with different clinical profiles and track biomarker profile changes over the course from normal aging to MCI to AD onset and progression
- Identify multimodal MRI, amyloid and tau PET profiles associated with AD onset and progression
- Determine critical factors that link cerebral Aβ deposition to neurodegeneration
- Identify genetic signatures influencing AD risk
- Compare findings with other populations having high and low risk for AD

ABC-DS Performance Sites

NiAD Sites

- University of Pittsburgh (coordinating center)
- University of Wisconsin, Madison
- University of Cambridge
- Washington University

ADDS Sites

- Columbia University (coordinating center)
- Harvard University
- University of California, Irvine

ABC-DS Planned Enrollment

NiAD

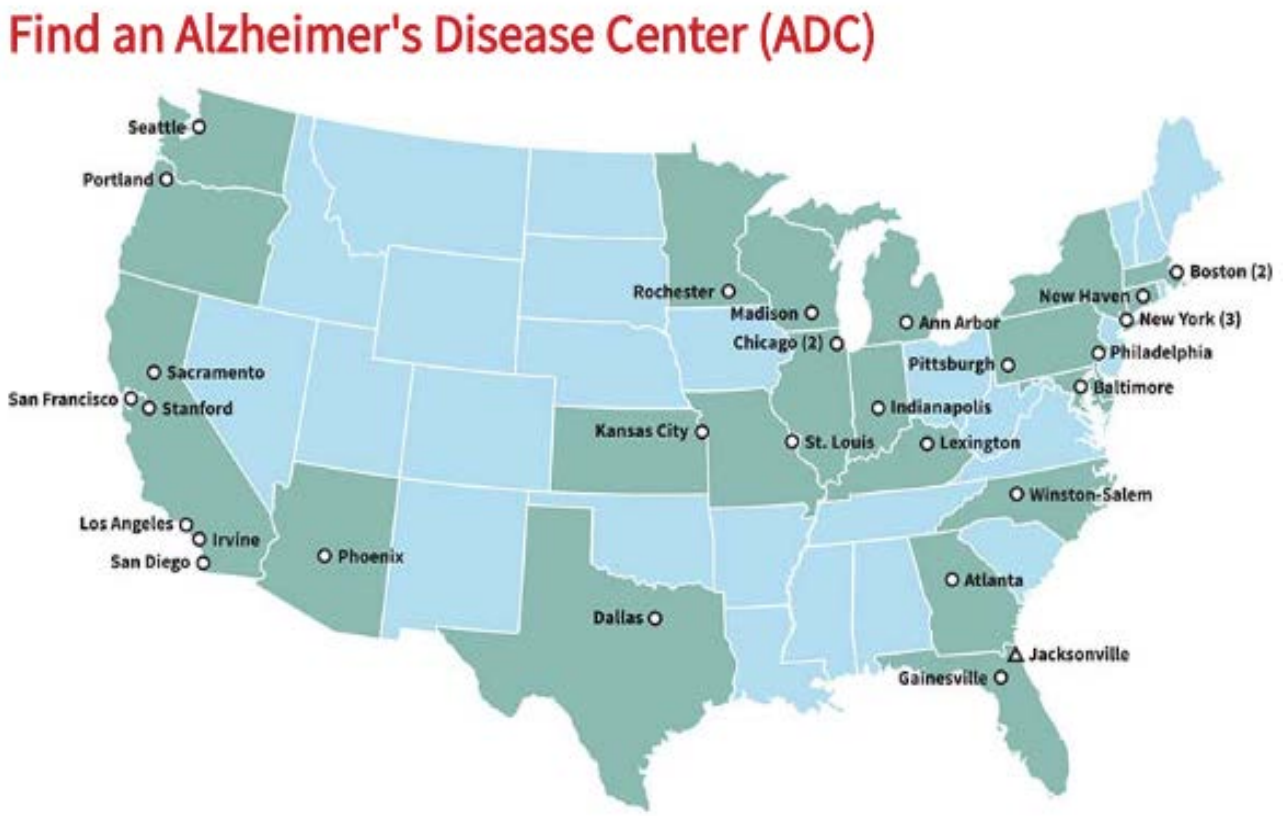
- 180 Subjects with DS (10% with AD)
- 40 Sibling controls
- age 25 and older

ADDS

- 200-225 Subjects with DS (25% with AD)
- Age 40 and older

Alzheimer's Disease Research Centers

- The NIA ADCs are NIH Centers of Excellence, established in 1984
- Areas of investigation range from:
  - the basic mechanisms of disease to
  - managing the symptoms and helping families cope with the effects
- ADC researchers conduct basic, clinical, translational and behavioral research and train scientists

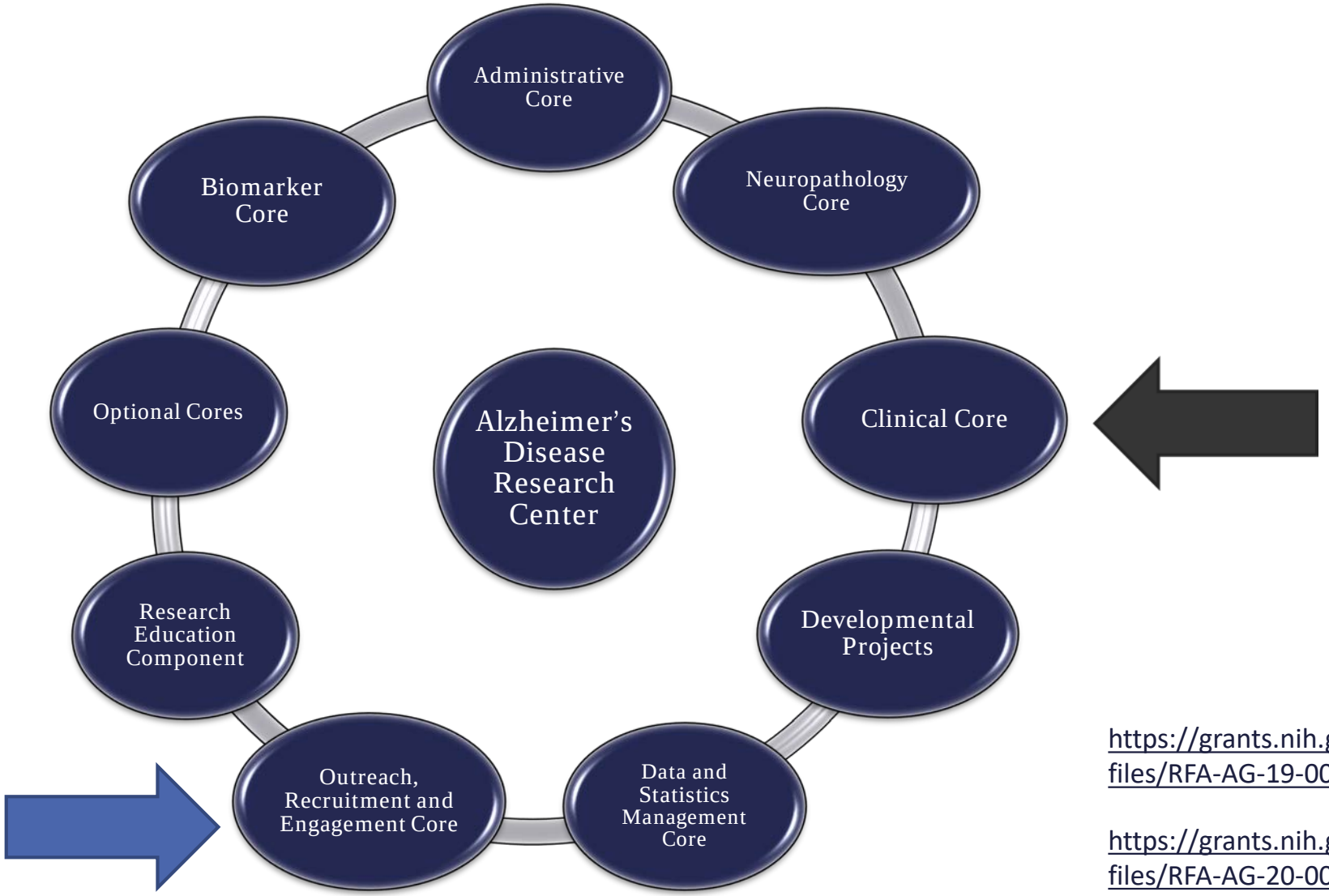


ADC Diverse Populations

- Underrepresented Groups
  - Rural (Oregon, Wash U, Wisconsin)
  - African American (e.g., Rush, Kentucky, Wash U)
  - Asian (UCSF)
  - Hispanic (e.g., UC Davis, Penn, Columbia)
  - Native American (Arizona, Wisconsin, UW, Wake Forest)

- Specific Populations
  - **Down Syndrome (Columbia, UC Irvine, Kentucky)**
  - Dominantly Inherited Alzheimer's Disease (DIAN study - Wash U)
  - FTLD (UCSF, Indiana, Mayo, Northwestern)
  - Oldest Old (UC Irvine)
  - English as a Second Language (Northwestern)

Alzheimer's Disease Research Center Structure



https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-19-001.html

https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-20-004.html

National Alzheimer's Coordinating Center Database of Uniform Data Set

	Uniform Data Set (UDS) (LONGITUDINAL)		Neuropathology Data Set (NP)		Minimum Data Set (MDS)
	UDS	FTLD Module	Data with associated UDS visit(s)	Data with no associated UDS visit (MDS only)	
Years covered	Sep 2005 – present	Feb 2012 – present	2005 – present	1984 – 2005	1984 – 2005
Study subjects	Enrollees followed at ADCs (with or without dementia)		UDS subjects who died and underwent autopsy	MDS-only subjects who died and underwent autopsy	Enrollees followed at ADCs (with or without dementia)
Approx # of subjects**	37,568	1,643	5,135	11,101	74,397
Approx # of variables	725	379	85		67
Method of data collection	Collected prospectively by clinicians, neuro-psychologists, and other ADC research personnel, using up to 18 standardized forms at each visit. Some forms also have Spanish-language and telephone versions.	Collected prospectively by clinicians, neuro-psychologists, and other ADC research personnel, using up to 13 standardized forms at each FTLD Module visit.	Standardized neuropathology form, completed by neuropathologist		Mainly abstracted retroactively from ADC medical records
Time period covered for each subject	Initial visit and each annual follow-up visit, plus milestones such as death or dropout	Initial FTLD Module visit and annual follow-up visit	Status of brain at autopsy		Mainly status on last ADC visit; some variables also capture initial-visit status
Topics covered (brief list)	Sociodemographics on subject and co-participant Family history Dementia history Neurological exam findings Functional status Neuropsychological test results Clinical diagnosis Imaging availability APOE genotype	Family history Neurological and motor exam findings Clinical bvFTD and PPA findings Neuropsychological test results Social norms Social behavior Co-participant questionnaires Imaging availability	Demographics Date of death Presence or absence of neuropathological features of most major dementias		Demographics Cognitive status Clinical diagnosis Selected clinical manifestations Comorbid conditions MMSE score Vital status

Unique features of ADC Program

- Very large number of geographically diverse, well-characterized, annually followed participants
- Longitudinal f/u
- Neuropathological data
- Many with imaging and genetic data also
- Two modules have been added to the UDS — 1) frontotemporal lobar degeneration (FTLD Module, implemented March 2015) and 2) Lewy body disease LBD Module, implemented August 2017)
- **Down Syndrome Module (DS Module) under development***

*INCLUDE Supplement

https://www.alz.washington.edu/WEB/data_descript.html

Alzheimer's Clinical Trials Consortium (ACTC) (U24)

- Awarded December 2017; ~$70 M
- PIs: **Paul Aisen**, Alzheimer's Therapeutic Research Institute (ATRI), San Diego; **Reisa Sperling**, Brigham and Women's Hospital and Massachusetts General Hospital, Boston; **Ronald Petersen**, Mayo Clinic, Rochester, Minnesota (U24AG057437)
- Includes multiple clinical trial sites with dedicated support
- A separate NIA Funding Opportunity Announcement (FOA) is soliciting applications for clinical trials to be managed and supported by the ACTC (PAR-18-513)

https://www.nia.nih.gov/research/dn/alzheimers-clinical-trials-consortium-actc

ACTC Goals:

- Conduct clinical trials (early to late stage) of promising **pharmacological and non-pharmacological interventions** for **cognitive and neuropsychiatric symptoms** in individuals with **AD and other age-related dementias** across the spectrum from pre-symptomatic to more severe stages of disease

- Provide a state-of-the-art clinical trial infrastructure to facilitate **rapid development and implementation of protocols**, including a **centralized Institutional Review Board (IRB)**

- Provide leadership in **innovative trial design methods, outcomes and analyses** as well as **recruitment strategies, particularly in diverse populations**

- Enable **broad sharing** of procedures and methods, as well as trial data and biosamples

ACTC-Down Syndrome Network (NIH INCLUDE Supplement)

Specific Aims

Leverage the extensive breadth and depth of expertise within ACTC and ABC-DS to efficiently conduct AD clinical trials in the DS population

1) Augment ACTC units with insights from leading experts in DS, including ABC-DS and European groups
2) Develop and facilitate sites capable of conducting AD clinical trial protocols in individuals with DS
3) Develop an electronic database for the ACTC-DS network that is harmonized with ABC-DS data standards

Slide courtesy of Michael Rafii with modifications

Other NIA/NIH Alzheimer's and Related Dementias Clinical Trial Mechanisms

- **Early Stage Clinical Trials for the Spectrum of Alzheimer's Disease and Age-related Cognitive Decline (R01) PAR-18-877**
  - Phase I and II, pharmacological and non-pharmacological interventions
  - Studies on trial design and methods

- **Late Stage Clinical Trials for the Spectrum of Alzheimer's Disease and Age-related Cognitive Decline (R01) PAR-18-878**
  - Phase II/III, III, pharmacological and non-pharmacological interventions

- **Advancing Research on Alzheimer's Disease (AD) and Alzheimer's-Disease-Related Dementias (ADRD): R43/R44 PAS-18-187 & R41/R42 PAS-18-188**

A Randomized, Placebo-Controlled, Dose-Escalating, Multicenter, Phase 1b Clinical Trial of the Anti-Amyloid Vaccine ACI-24 in Adults with Down Syndrome

3 Star Study

- AG047922 - supported by NIA, LuMind Foundation and AC Immune
- ACI-24: Anti-amyloid active vaccine; currently in phase 2 for sporadic AD in Europe
- Aims to stimulate the immune system (without concomitant pro-inflammatory T cell activation) to produce antibodies that specifically target the oligomeric and fibrillary Abeta proteins to prevent plaque accumulation and to enhance plaque clearance
- 3 clinical trial sites – Barrow, MGH, UCSD
- The first (low-dose) and the second (high-dose) cohorts fully enrolled

Slide courtesy of Michael Rafii with modifications

3 Star Study Design

- Phase I (safety and tolerability)
- Participants aged 25-45 with DS, IQ>40
- 2 cohorts (low dose, high dose) of 8 subjects each (n=16, 12 active treatment, 4 placebo)
- 12 months treatment and 12 months safety follow-up
- All participants have been able to complete all study procedures
- Topline results expected late 2020
- Optional cohort 3 expansion: additional 8 subjects based on safety, tolerability, immunogenicity or target engagement data

Slide courtesy of Michael Rafii with modifications

Thank You!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Take confidential health-related surveys. These surveys are aimed at better understanding of the health of people with Down Syndrome across their lifespans.
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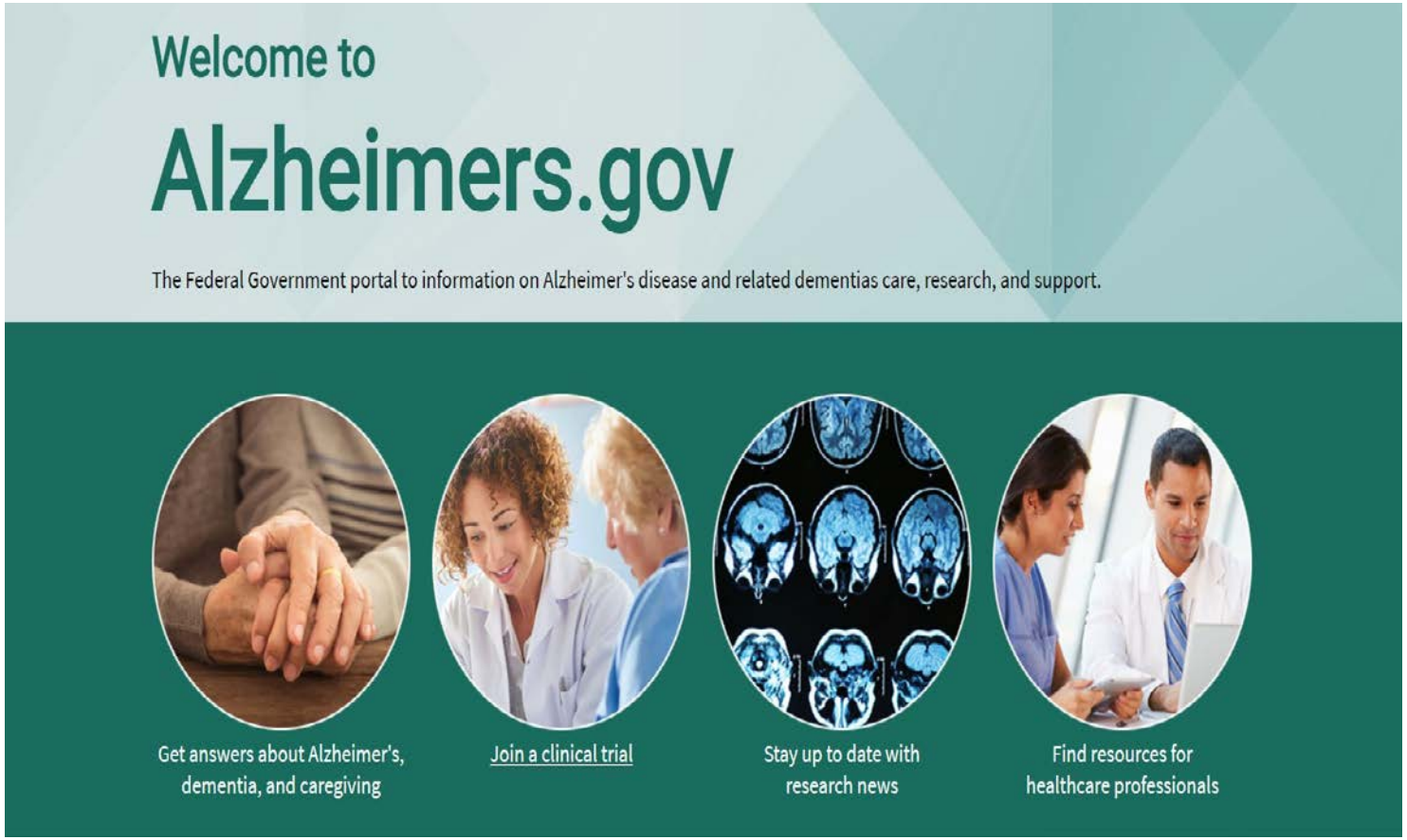
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