The NIH INCLUDE Project

(INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE)

117th Meeting of the Advisory Committee to the Director (ACD)
National Institutes of Health
Friday, December 14, 2018

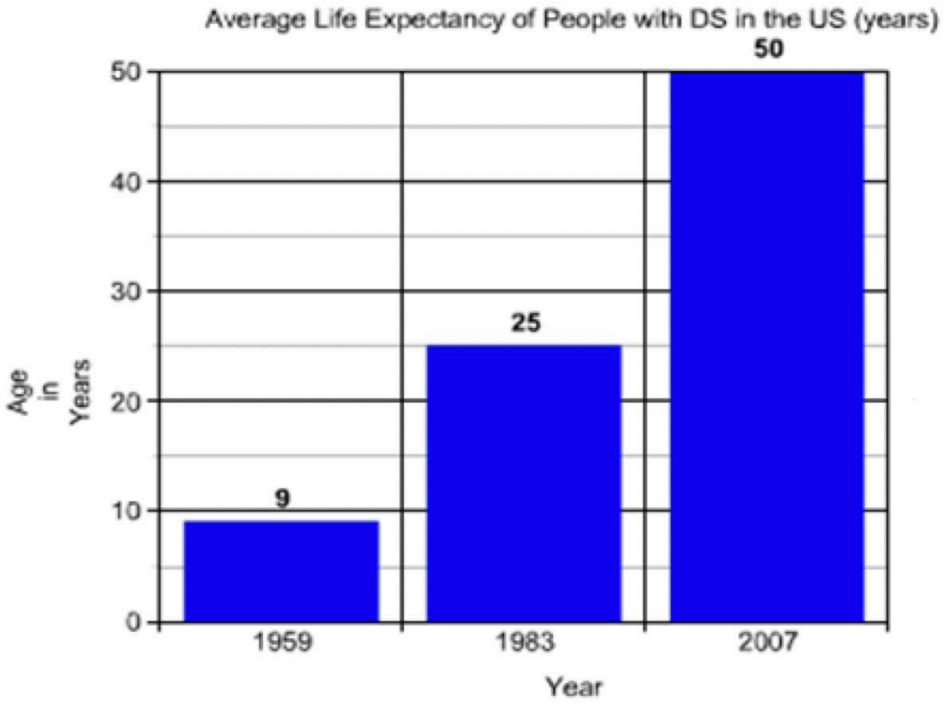
Diana W. Bianchi, MD
Director, National Institute of Child Health and Development
Gary H. Gibbons
Director, National Heart Lung and Blood Institute
Lawrence A. Tabak, DDS, PhD
Principal Deputy Director, NIH

Mr. Frank Stephens' testimony to the House Appropriations Committee on October 25, 2017

https://www.youtube.com/watch?v=yQJEoRhkapw

The case for research in Down syndrome

- Each year, ~ 6000 infants with Down syndrome born in U.S.
- Lifespan for people with Down syndrome has doubled in 25 years



Source: Presson AP et al. *J Pediatr*. 2013 October ; 163(4): 1163–1168.

New Opportunity for NIH on Down Syndrome

- 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:

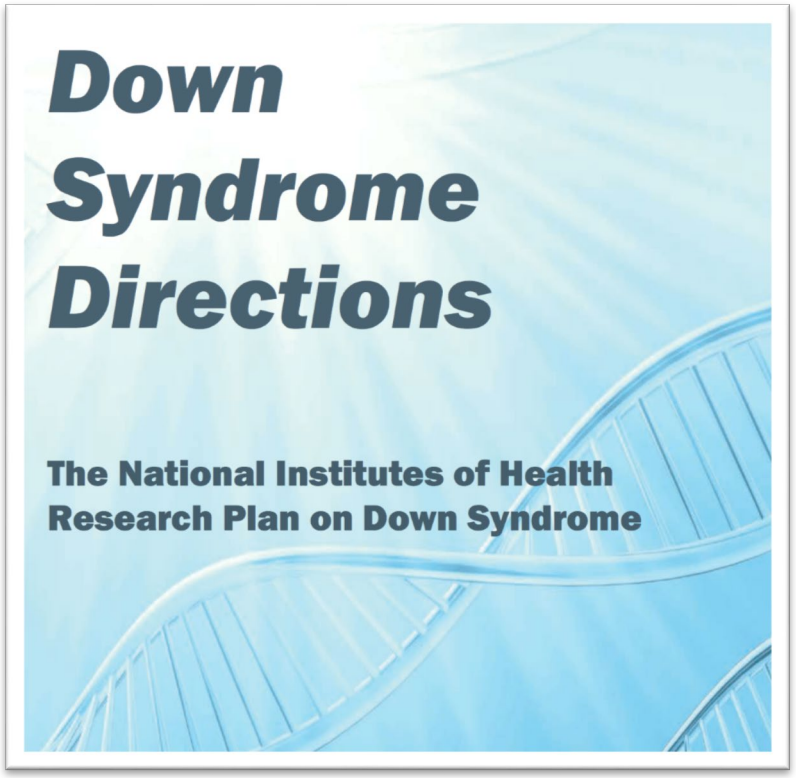
  - Alzheimer's disease
  - Leukemia
  - Heart defects
  - Immune system dysregulation
  - Autism
  - and other conditions…"

Protected from:
- Many cancers
- Heart disease and heart attacks

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

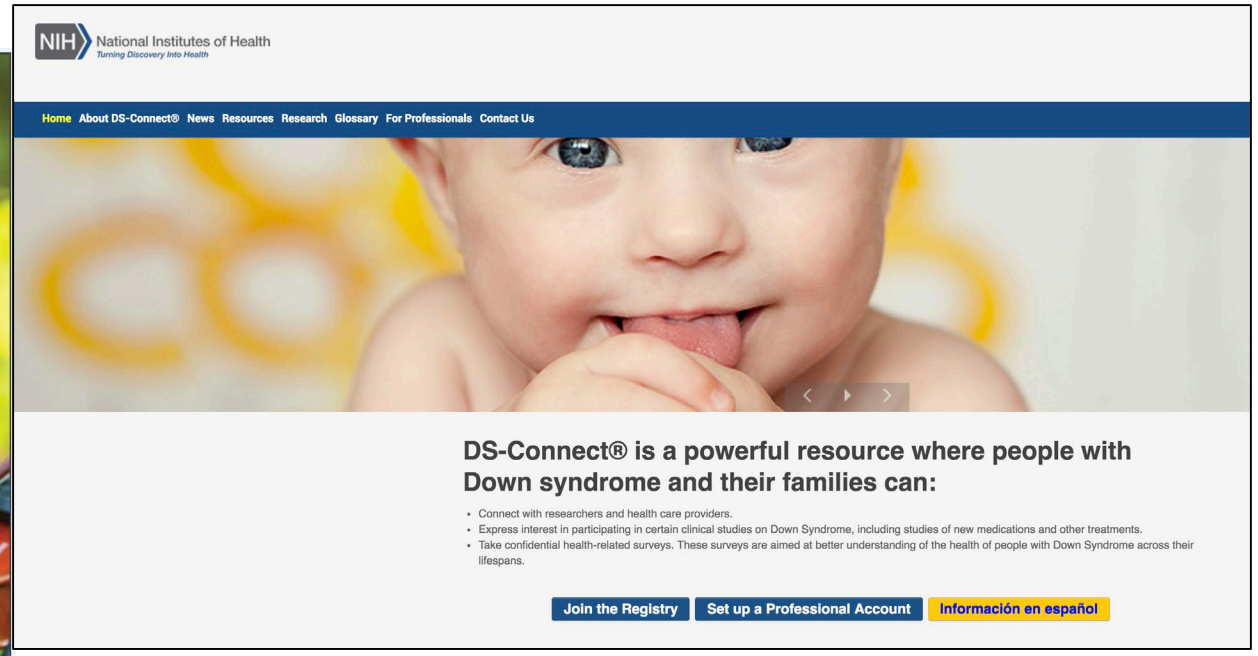
NIH Research Plan on Down Syndrome: Down Syndrome Directions

- Updated in 2014
- Goal: Develop research goals and objectives for NIH research
- 5 priority areas identified:
  - Pathophysiology of Down Syndrome and Disease Progression
  - Screening, Diagnosis and Functional Measures
  - Treatment and Management
  - Research Infrastructure
  - Down Syndrome and Aging



NIH National Institutes of Health
Down Syndrome Working Group

NIH Resource for individuals with Down syndrome: DS-Connect®



Launched Sept. 6, 2013 by NICHD

URL: http://DSConnect.nih.gov

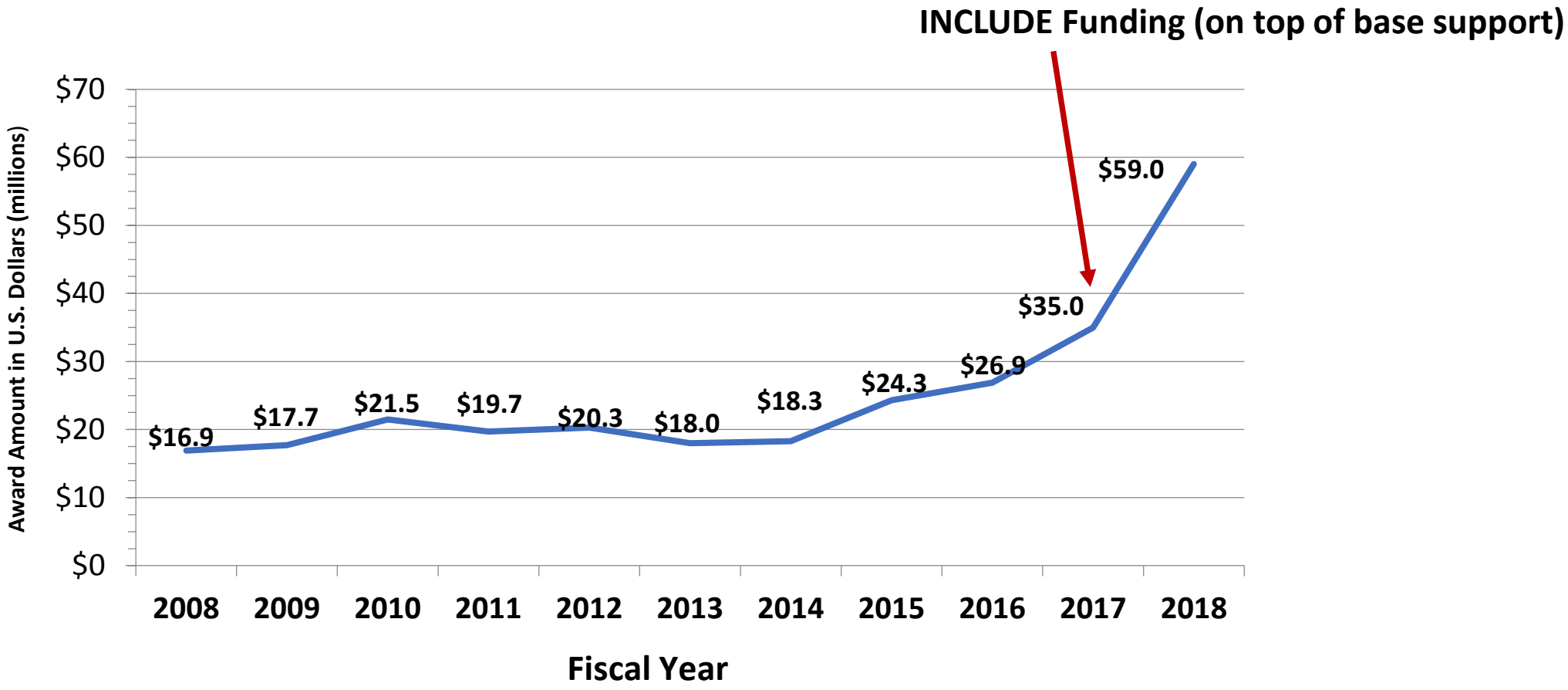
Partnership through the Down Syndrome Consortium

NIH convened in July and November to engage on the INCLUDE Project

New Opportunity for NIH on Down Syndrome: FY18 Kick-Off

- Spring 2018:
  - Established NIH INCLUDE Steering Committee
  - Coordinated through Trans-NIH Down Syndrome Working Group (13 NIH Institutes)
- June 20: Project announced by Congressional offices
- June 20: NIH Research Plan for INCLUDE and funding notices released
- July 23: Applications received by NIH
- October 1: Fiscal Year 2018 awards announced
- November 7: First workshop held “Alzheimer’s Disease Clinical Trials in Down Syndrome Planning Meeting“

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



The NIH INCLUDE Project: FY18 Kick-Off

- "Leave no stone unturned" approach to actively solicit supplement applications
- Dual solicitations
  - Expansion of a currently-supported Down syndrome project
  - Amend or augment an existing project to *add a Down syndrome component (e.g. biological samples, trial participants)*
- Latter strategy may draw fresh perspective into the Down syndrome research community
- Begins to address need to include individuals with Down syndrome into ongoing clinical research

National Institutes of Health
Turning Discovery Into Health

Search NIH

NIH Employee Intranet | Staff Directory | En Español

Health Information | Grants & Funding | News & Events | Research & Training | Institutes at NIH | About NIH

Home » Research & Training » Medical Research Initiatives

THE INCLUDE PROJECT

The INCLUDE Project Research Plan

(INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndrome)

On this page

Introduction

INCLUDE Project Research Plan

Thinkstock

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

The NIH INCLUDE Project
Research Plan

3 components to address key quality-of-life issues
for individuals with Down syndrome and their families:

1. Targeted, high-risk, high-reward basic science studies on chromosome 21

2. Build a large cohort of individuals with Down syndrome for comprehensive analysis and biomarker evaluation

3. Include individuals with Down syndrome in existing and future clinical trials

Fiscal Year 2018 INCLUDE Funding

- **$22.2 M supported 49 awards**
- 14 NIH Institutes participating
- Addressed all 3 INCLUDE plan components
- Data sharing expectation

Funding Opportunities

Funded Projects

- The Alzheimer's Clinical Trial Consortium - Down Syndrome Network (ACTC- DSN)
- Neurodegeneration in Aging Down Syndrome (NiAD): A Longitudinal Study of Cognition and Biomarkers of Alzheimer's Disease
- Identification of optimum spectacle prescriptions for patients with Down syndrome
- Neurobehavioral Research on Infants at Risk for Language Delay and ASD
- MRI & CT studies of the developing vocal tract
- National Alzheimer's Coordinating Center (NACC)
- Treating with Gamma-Secretase Modulators to Prevent Neurodegeneration in Mouse Models of Down Syndrome and Alzheimer Disease
- Biomarkers of Alzheimer's Disease in Adults with Down Syndrome (ADDS)
- Mechanisms of white matter development in Down syndrome
- Data Fusion: A Sustainable, Scalable, Open Source Registry Advancing PVD Research
- Generation of isogenic trisomy 21 iPSC resource
- A Computational Biomechanical Airway Model for Obese Children at Risk for OSAS
- Human ISG15 and USP18 deficiencies underlying type-I interferonopathies
- Mechanisms of IL-6 mediated T cell pathogenesis in autoimmunity
- Genome-wide search for inborn errors of IL-17 immunity underlying chronic mucocutaneous candidiasis
- Dimensional Analysis of Developmental Brain Disorders using an Online, Genome first Approach/Dimensional, Sleep, and Genomic Analyses of Down Syndrome to Elucidate Phenotypic Variability

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

INCLUDE Component 1

Targeted, high-risk, high-reward basic science studies

Emerging scientific areas:

- Examine the roles of multiple genes on chromosome 21 simultaneously
- Explore chromosome silencing
- Evaluate epigenetic/ metabolomic/ transcriptomic profiling in model organisms/iPSCs/brain organoids in several model systems
- Develop novel model systems, including a molecular atlas for cardiac and other specimens

Emphasis on studies that can inform the other two components for a cohesive approach and have potential for clinical translation

INCLUDE Component 1: A Few Examples of Funded Studies

Targeted, high-risk, high-reward basic science studies

- Mechanisms of white matter development in Down syndrome (PI: Tarik Haydar, NINDS)
- Mechanisms for cell signaling in the control of cardiomyogenesis (PI: Kunhua Song, NHLBI)
- A Novel Approach to Molecular Cell Pathologies of Human Down Syndrome and DS-AD (chromosome silencing) (PI: Jeanne Lawrence, NICHD)
- Treating with Gamma-Secretase Modulators to Prevent Neurodegeneration in Mouse Models of Down Syndrome and Alzheimer Disease (PI: Bill Mobley, NIA)

INCLUDE Component 1: A Few Examples of Funded Studies

Targeted, high-risk, high-reward basic science studies

- Generation of isogenic trisomy 21 iPSC resource (PI: Anita Bhattacharyya, NICHD)
- Mechanisms of IL-6 mediated T cell pathogenesis in autoimmunity (PI: JH Buckner, NIAID)
- DYRK1A signaling in control of cell growth, proliferation and DNA damage repair (PI: Larisa Litovchick, NIAID)

INCLUDE Component 2: A Few Examples of Funded Studies

Assemble a large cohort for pan-'omics and biomarker studies

- Two Gabriella Miller/Kids First Studies (NIH Common Fund with NHLBI, NCI and NICHD)
  - Genomic Analysis of CHD and ALL in Children with Down Syndrome
  - Germline and Somatic Variants in Myeloid Malignancies in Children
- Alzheimer's Biomarkers Consortium-Down syndrome multi-site projects (PIs: Handen, Schupf, NIA)
- Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Center at Vanderbilt University-ASD cohort that would expand to Down Syndrome (PI: Neul, NICHD)
- Clinical Evaluation of Pulmonary Hypertension in Down syndrome-pediatric cohort would expand to Down syndrome (PI: Abman, NHLBI)

Emphasis on building cohort across life stages to address key health and quality-of-life issues

INCLUDE Component 3

Build a clinical trials network for inclusion in existing and future clinical trials

- Extremely limited medication trials in DS have been underpowered and lacked efficacy
- Need to test how commonly used medications affect people with Down syndrome
- Need to develop clinical measures appropriate for Down syndrome

Emphasis on building clinical research resources to achieve full inclusion now and in the future

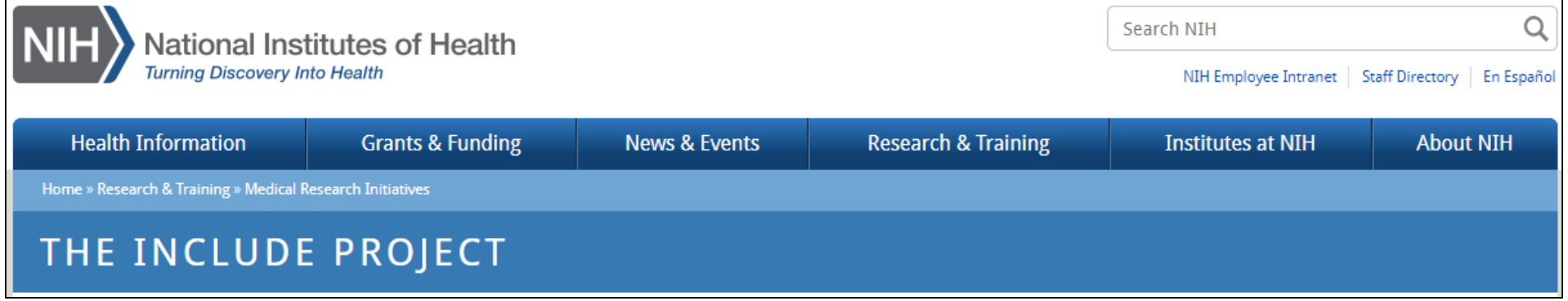
INCLUDE Workshop "Alzheimer's Disease Clinical Trials in Down Syndrome" Planning Meeting

- Alzheimer's Disease is major concern among Down syndrome community
- Held November 7 at NIH, coordinated with NICHD and NIA
- Down syndrome and Alzheimer's Disease advocacy communities participated
- Investigators engaged in clinical trials and cohort studies of Alzheimer's Disease and/or Down syndrome

INCLUDE Component 3: A Few Examples of Funded Studies

Build a clinical trials network for inclusion in existing and future clinical trials

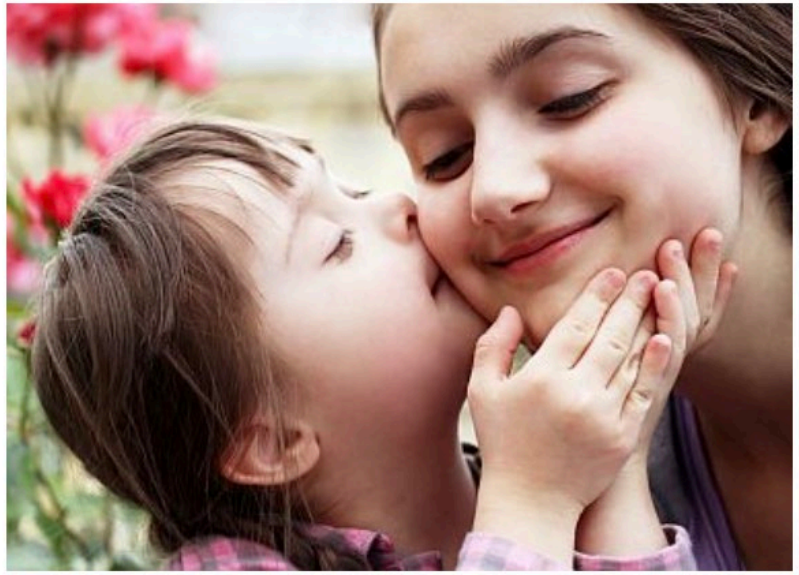
- Alzheimer's Clinical Trial Consortium (ACTC): Develop clinical trials network for clinical trials on Alzheimer's Disease in Down syndrome (PI: Aisen, NIA)
- Extending the Early Start Denver Model to Children with Down Syndrome: bringing children with Down syndrome into ongoing trial on early intervention in ASD (PI: Robins, NIMH)
- Impact of Treatment of mild sleep-disordered breathing on children's health: bringing children with Down syndrome in to ongoing trial in pediatric sleep apnea (PIs: Furth and Redline, NHLBI)



2019 Support and beyond:

- FY19 Funding Opportunity Announcements planned
- Workshops in development for early 2019:
  - o "Planning a Virtual Down syndrome Cohort across Lifespan"
  - o "The State of the Science for Meaningful Clinical Trials in Down syndrome"

INCLUDE Project Research Plan



Thinkstock

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

INCLUDE Steering Committee

Diana Bianchi, Co-chair

Anna Mazzucco, Office of the Director, NIH
Lawrence Tabak, Office of the Director, NIH

Gary Gibbons, Co-chair

Trans-NIH Working Group on Down Syndrome

Melissa Parisi
NICHD

Gail Pearson
NHLBI

Lisa Kaeser
NICHD

Robert Riddle
NINDS

Charlene Schramm
NHLBI

Donna Krasnewich
NIGMS

Sujata Bardhan
NICHD

Nina Schor
NINDS

Malcolm Smith
NCI

Laurie Ryan
NIA