

# Progress on the INCLUDE Project at the National Institutes of Health (NIH): Advancing Cohort Studies and Clinical Trials in Down Syndrome

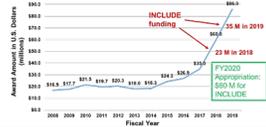
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## BACKGROUND

A Congressional directive in fiscal year (FY) 2018 appropriations legislation called for a new trans-NIH research initiative on critical health and quality-of-life needs for individuals with Down syndrome (DS). Consequently, the NIH launched a new DS research initiative known as **INCLUDE** (Investigation of Co-occurring conditions across the Lifespan to Understand Down syndrome); <https://www.nih.gov/include-project>. INCLUDE will investigate conditions that affect individuals with DS and the general population, such as Alzheimer's disease (AD), autism, cataracts, celiac disease, congenital heart disease (CHD), and diabetes.

### NIH Funding for Research on Down Syndrome



## INCLUDE OBJECTIVES

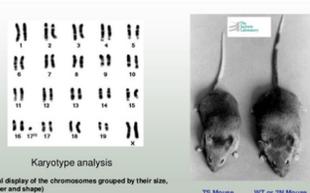
- Conduct targeted, high-risk, high-reward basic science studies on chromosome 21.**
    - Study animal models of DS
    - Explore the effects of multiple genes triplicated on chromosome 21 simultaneously
    - Identify pathways that may be most responsive to new therapies.
    - Explore ways to "silence" the extra copy of chromosome 21
  - Assemble a study population of individuals with DS.**
    - Add to or expand existing DS cohorts with "omics data"
    - Develop shared databases using common data elements
    - Build on the DS-Connect® registry
  - Include individuals with DS in existing and future clinical trials.**
    - Bolster recruitment of people with DS in clinical trials for co-occurring conditions
    - Develop new therapies for DS
    - Leverage existing clinical trials infrastructure to explore differences in drug metabolism in those with DS and provide assistance in clinical trial design and training for conducting drug trials in people with DS.
    - Expertise from the DSMIG membership will be essential to inform these efforts
- Many Funding Opportunities available for FY20-FY22 R01, T-R01, R21, R61/R33, Competitive Supplements, Administrative Supplements, COVID-19, etc.

See URL: <https://www.nih.gov/include-project>

## Component 1: Basic Science Research

### Mouse models

**Ts65Dn mouse:** Developed by The Jackson Laboratory Extra material derived from mouse chromosome 16 and 17 Mice: DD, hyperactive, poor growth, facial features, reduced fertility, develop amyloid plaques



Side compliments of H. Craig Heller

### Examples of INCLUDE-funded mouse studies

- Novel approach to silencing chromosome 21 in mouse models of Down syndrome to rescue AD phenotype in Ts65Dn
- Age-related immune system alterations, epigenetic changes, loss of hearing, cognitive decline and behavioral changes in three different DS mouse models (Dp16, Dp10, and Dp16 disomic for APP)

### Studies in induced pluripotent stem cells (iPSC)

- Investigate the gene dosage imbalance in DS, and provide a well-defined set of isogenic DS iPSC for investigators
- Epigenetic silencing of human chromosome 21 in DS organoid cultures
- Mitochondrial fusion and function in DS cell lines
- Role of overexpression of cardiac-specific, dosage-sensitive trisomic genes on chr21 in development of heart defects

### Other basic science studies

- Role of global RNA polymerase II dysregulation in DS
- Ancestral roles of histone-modifying genes in heart development and disease in a Drosophila model of DS
- Studies on the molecular regulation of IFN-1 in DS, to develop therapies for DS-associated immune disorders

## Component 2: Cohort Development

### Examples of INCLUDE-funded studies

- Study speech recognition in children with DS and hearing loss
- Conduct on-line cognitive assessments (Self-Determination Inventory) via DS-Connect in the PCORnet population
- Study the impact of CHD repair on neurodevelopmental and behavioral outcomes at 3-5 years of age
- Incorporate approximately 2,000 existing DNA samples collected from individuals with DS into the Kids First Data Resource Center
- Develop culturally and linguistically appropriate educational and recruitment materials for African Americans with DS
- Characterize unique comorbidity patterns in people with DS
- Validate a behavioral measure of executive function as a resource for future clinical trials in DS.

## Component 2: Cohorts via DS-Connect®

### DS-Connect®: The Down Syndrome Registry

A secure, confidential, online survey tool to collect basic health information about people with DS and connect them with research opportunities.



DS-Connect® is a powerful resource where people with Down syndrome and their families can:

- Connect with researchers and health care providers
- Express interest in participating in other clinical studies or clinical trials, including studies of new medications and other treatments
- Help coordinate health-related services. These services are aimed at better understanding of the health or genetic condition someone has

[Join the Registry](#) [Set up a Professional Account](#) [Information in Spanish](#)

<https://DSConnect.nih.gov>

See DSMIG poster, Bardhan et al.

### In the past 5 years:

- 51 studies have requested recruitment support\*
  - 46 studies have been approved by the Research Review Committee (91% success rate)
  - 9 INCLUDE projects have received recruitment support
- \*Requires submission of a summary of protocol, purpose and IRB Status and review by the Research Review Committee for approval

### Workshop: "Planning a Virtual DS Cohort Across the Lifespan"

Hosted by NIH on Sept. 23-24, 2019 Brought together clinicians, researchers, advocates, self-advocates, data scientists to learn from existing DS cohorts to inform future ones Key principles to address:

- Data Standardization and Harmonization for data/specimen collection
- Community Outreach Efforts—see DSMIG poster, Cohen et al.
- Clinical Trial Readiness Issues

A Data Coordinating Center for INCLUDE cohort data and biospecimens will be awarded in 2020

## Component 3: Clinical Trials

### Examples of INCLUDE-funded Clinical Trials

- Study safety and effects of tofacitinib, a JAK inhibitor, on immune-mediated skin conditions in young adults with DS
- Evaluate assessment and medication treatment of ADHD in children with DS
- Interventions to enhance CPAP adherence in children/adolescents with DS and obstructive sleep apnea (OSA)
- Medications for obstructive sleep apnea to improve cognition in children with DS
- Clinical trials to prevent Alzheimer's Disease in DS

## Component 3: Clinical Trials Support

### The NICHD Pediatric Trials Network (PTN)

- PTN clinical research sites are located at over 100 universities and children's hospitals across the U.S.
- A Coordinating Center/Operations Core is located at Duke Clinical Research Center
- The PTN will partner with INCLUDE to support drug studies in Down syndrome, with a training objective



## CONCLUSIONS

- The new trans-NIH INCLUDE initiative is making major investments in DS research, in basic science, cohort development, and clinical trials domains
- DS-Connect® is a powerful online registry that facilitates recruitment of families to research studies
- INCLUDE is creating a blueprint for developing a DS cohort across the lifespan using data and biospecimen harmonization and linkages
- The Pediatric Trials Network is leading a DS clinical trials program as part of the INCLUDE initiative

## Down Syndrome Consortium

