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

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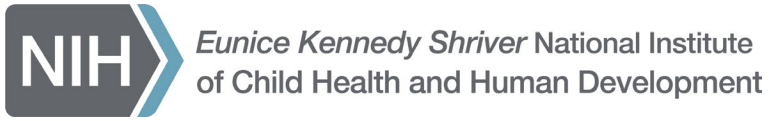


Presentation Outline

- Background
- INCLUDE Accomplishments
  - Basic Science
  - Cohort Development
  - Clinical Trials
  - Data Resources
  - Workforce Development
- Summary

Background

- Each year, approximately **6,000 babies** in the U.S. are born with Down syndrome (DS), affecting approximately **1 out of every 700 births.**
- In part because of research that resulted in better treatments for infants born with DS and congenital heart disease or leukemia, the **average lifespan** for a person with DS has doubled from 30 to 60 years.
- People with DS are more likely to have some health conditions like **Alzheimer's disease** while being highly protected from others like many forms of **cancer and coronary artery disease**.
- There is an increasing need for research focusing on improving the quality-of-life for individuals with DS **across the lifespan**.

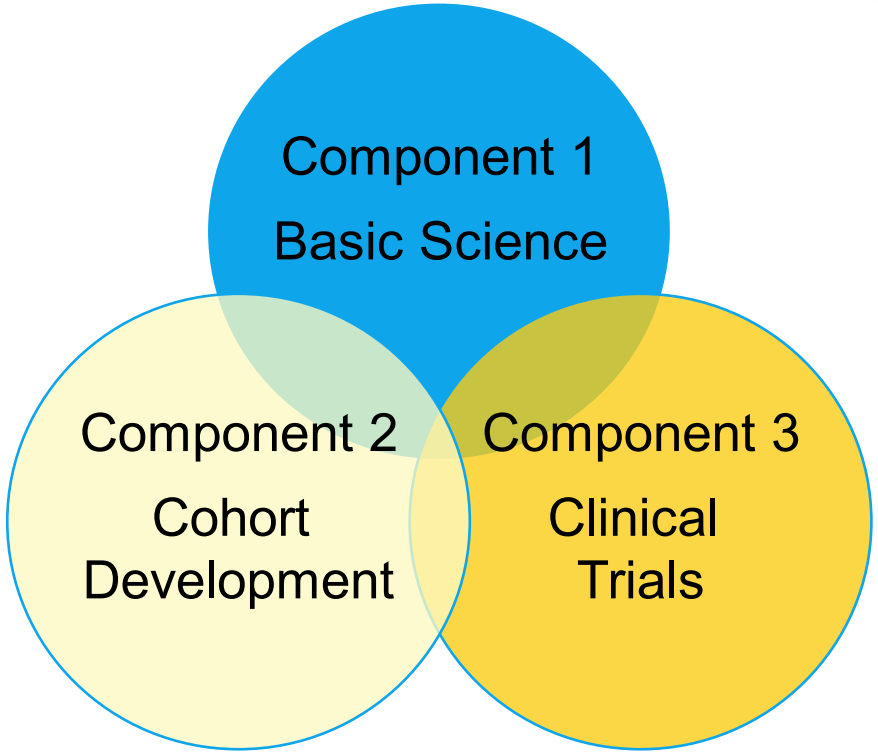
FY18 Congressional Support for INCLUDE

"…the Committee encourages NIH to pursue a multi-year, trans-NIH research initiative examining immune system dysregulation and trisomy 21, with the aim of yielding scientific learnings that could significantly improve the health of individuals with Down syndrome as well as millions of typical individuals."

Mr. Frank Stephens, Congressional Testimony 2017

Three Components of INCLUDE Project

1. Conduct 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**.

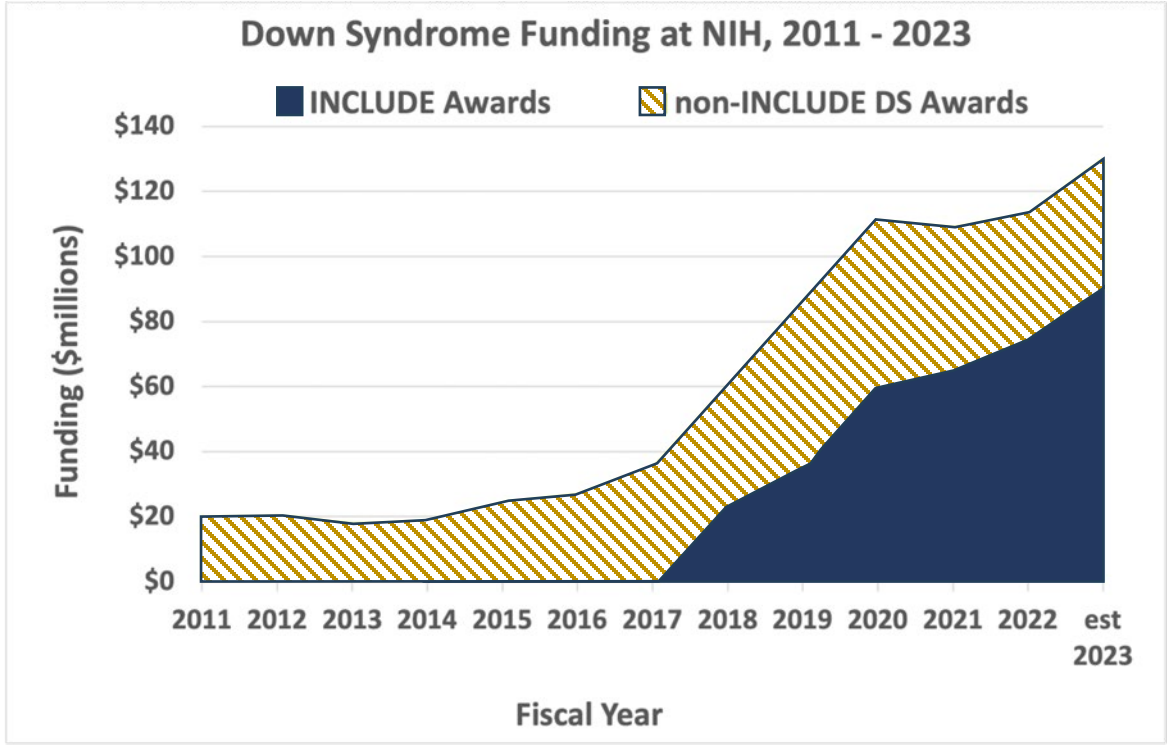


INCLUDE Applies Expertise and Resources from 18 NIH ICs to Collaboratively Advance DS Science

- The INCLUDE project will:
  - **Investigate conditions** that affect individuals with DS and the general population, such as Alzheimer's disease, autism, cataracts, celiac disease, congenital heart disease, and diabetes.
  - **Increase the number of investigators/trainees** studying DS.
  - Engage with those with DS and their families from **diverse backgrounds** to participate in ongoing research.

Down Syndrome Funding at NIH

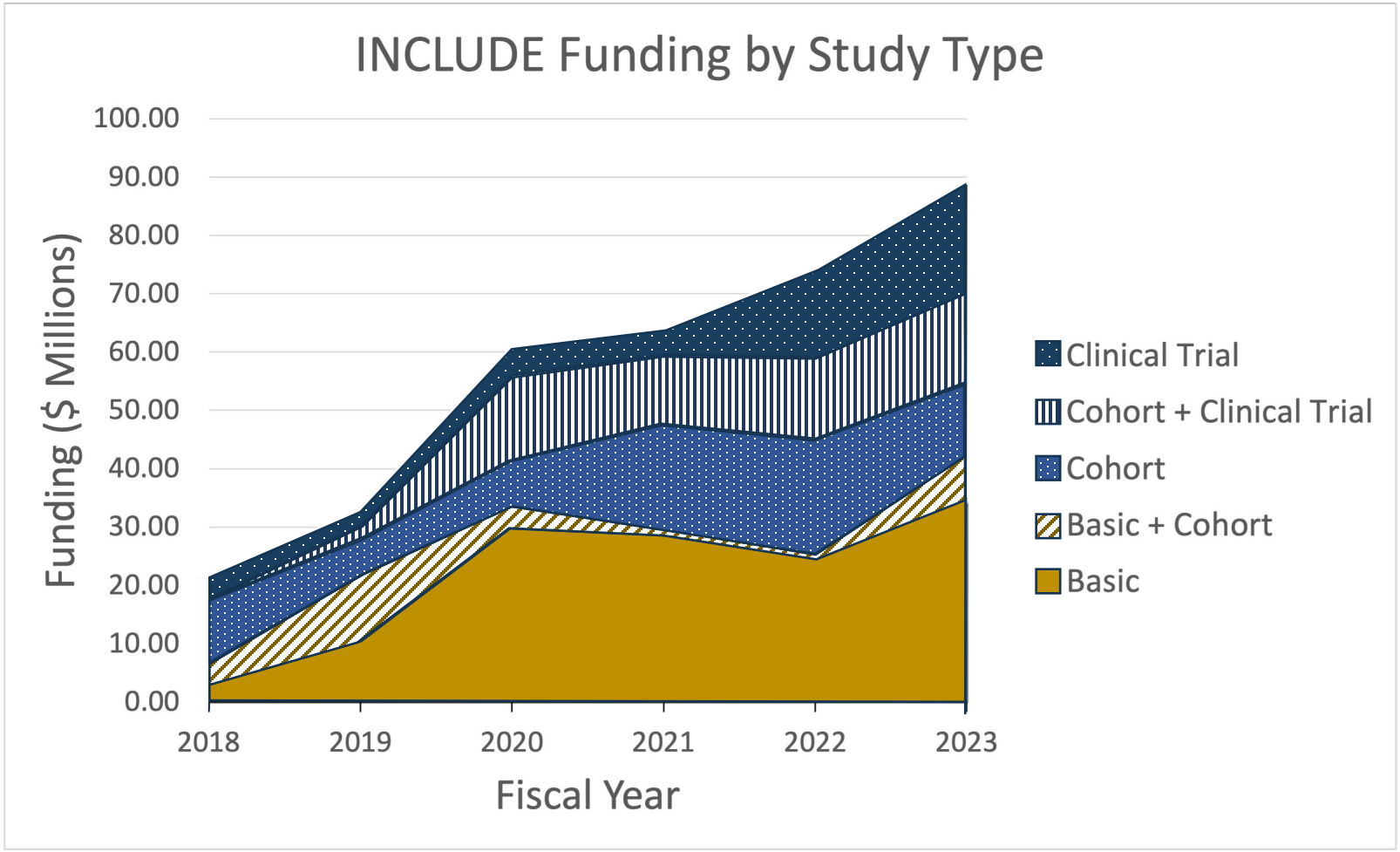
FY	INCLUDE ($M)	Non-INCLUDE DS ($M)	Total DS ($M)
2018	23	37	60
2019	35	51	86
2020	60	51	111
2021	65	44	109
2022	75	38	113
2023	90	40	133



The NIH has invested **$348 million** over the past **6 years** on **INCLUDE**

Awards in Support of INCLUDE Research

- The majority of INCLUDE funds support basic and high-risk discovery research studies
- The number of cohort studies and clinical trials supported by INCLUDE has increased every year



What Has INCLUDE Accomplished So Far?
Basic Science

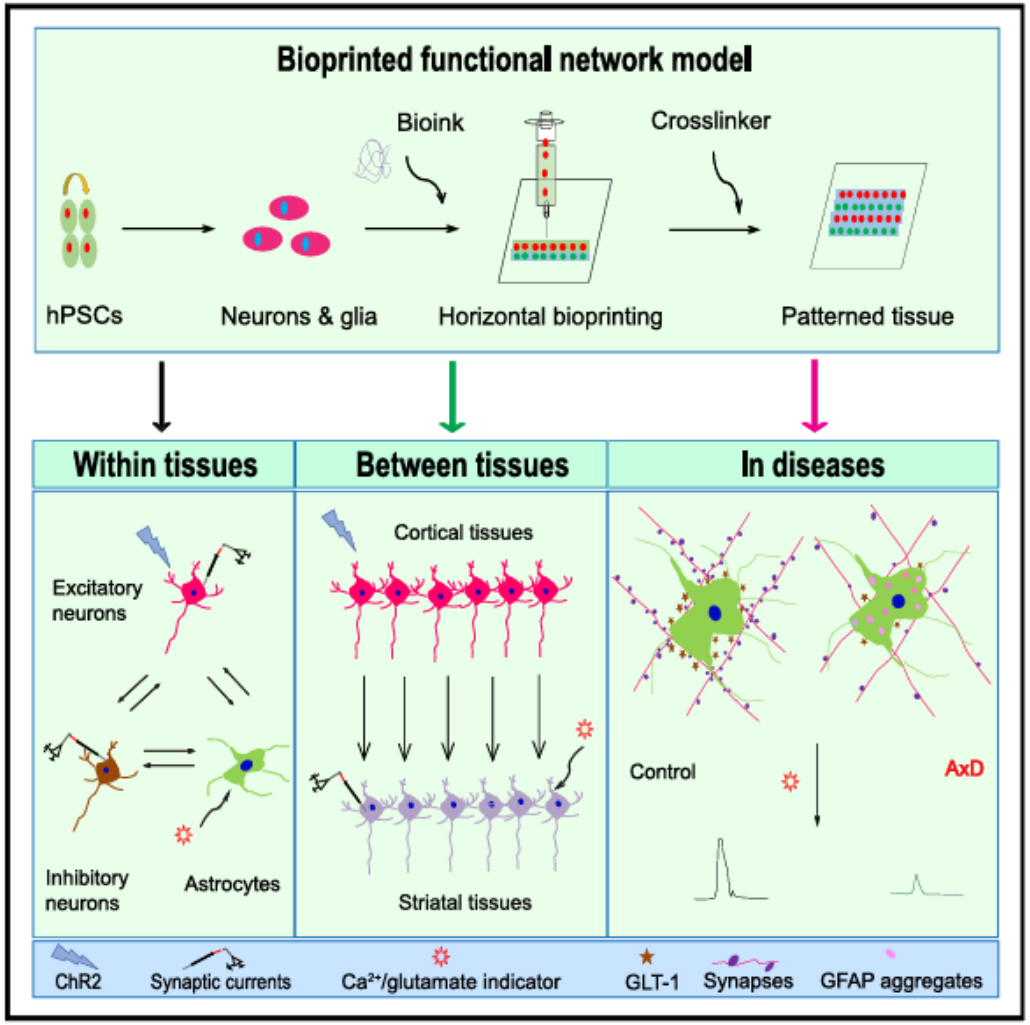
- Developed **new models** to study DS
  - Animal models
  - Induced pluripotent stem cells (iPSCs)
- **Biomarkers** (e.g., Alzheimer's disease)
  - Identify risk factors
  - Precision medicine approaches for clinical trials
- **Co-occurring conditions**
  - Alzheimer's disease, sleep apnea, congenital heart defects, and leukemia

What Has INCLUDE Accomplished So Far?
Basic Science Findings

- Small changes in the **dosage of many genes** on an entire chromosome had a cumulative effect on the features of DS in an individual
- Identified genes that may contribute to **congenital heart disease** in infants with DS
- Identified **biomarkers of neurodegeneration** and risk and resilience factors for **Alzheimer's disease** through the **Alzheimer's Biomarkers Consortium – Down Syndrome (ABC-DS)**

3D Bioprinting of Human Neural Tissues with Functional Connectivity

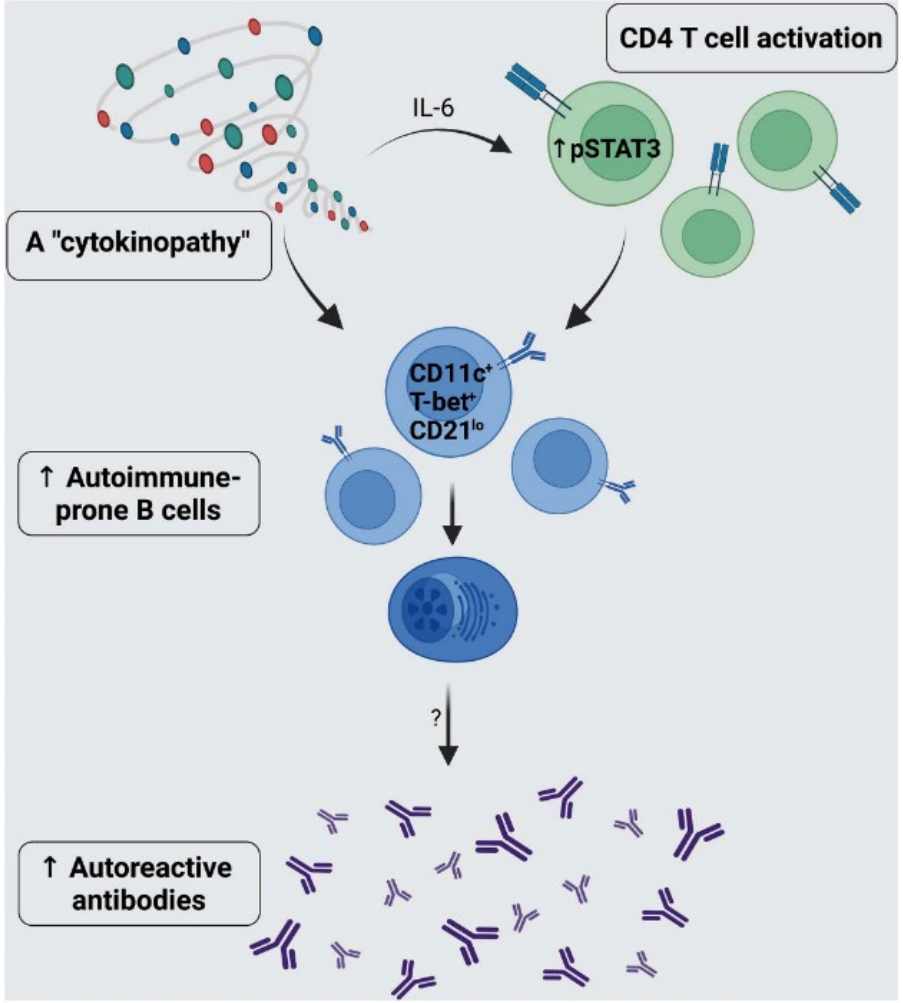
- Need for better model systems to help understand DS neural pathology
- Developed a 3D bioprinting platform utilizing defined human neural cell types and a commercial bioprinter
- 3D model exhibited functional human neural tissues with neural circuits between defined neural subtypes and functional connections between cortical-striatal tissues
- Demonstrated disease-relevant functional phenotype using iPSCs from a person with Alexander disease in the bioprint model
- Designed neural tissues may be useful in modeling DS disease pathology



Yan Y, et al. Cell Stem Cell. 2024. PMID: 38306994 doi: 10.1101/2024.01.18.576289.

Mechanism of Elevated Autoimmunity in Down Syndrome

- Individuals with DS are prone to severe infections and autoimmune conditions (e.g., thyroiditis, type 1 diabetes, celiac disease, alopecia areata)
- Researchers investigated mechanisms underlying autoimmune susceptibility by mapping soluble and cellular immune landscape
  - Persistent elevation of up to 22 cytokines at steady state
  - DS autoimmunity-prone state characterized by cytokinopathy, hyperactivated CD4 T cells, and ongoing B cell activation
- Possible therapeutic avenues include both broad immunosuppressants like Jak inhibitors and more targeted approaches such as IL-6 inhibition



Breaking Immune Tolerance in Down Syndrome: A Triad of Cytokines, Activated T cells and CD11c+ B Cells. Created with BioRender.

Malle, et al. *Nature* volume 615, p. 305–314 (2023)

What Has INCLUDE Accomplished So Far?
Cohort Development

- Alzheimer's Biomarker Consortium – Down Syndrome [ABC-DS] (92 investigators across 19 institutions)
  - Identified biomarkers of neurodegeneration and risk and resilience factors for Alzheimer's disease in a cohort of 600+ adults with DS
    - Study examples:
      - Longitudinal analysis of tau positron emission tomography (PET) in individuals with DS
      - Estimating emergence of amyloid and tau burden in DS
- Co-enrolling subjects in the Trial-Ready Cohort-Down Syndrome (TRC-DS) that will recruit for Alzheimer's clinical trials

ABC-DS
Alzheimer Biomarker Consortium-Down Syndrome

INCLUDE Cohort Development Program

Down syndrome Cohort Development (New in 2024!)

- A prospective cohort of people with DS to undergo **comprehensive deep phenotyping and biosample acquisition under a common protocol**
- **Collection and sharing of demographic, clinical, laboratory, and imaging data through a new clinical coordinating center**
- **Biospecimen acquisition and sharing**

Data will be shared with and made available through the **INCLUDE DCC**

What Has INCLUDE Accomplished So Far?
Clinical Trials

- Investigated the **impact of COVID-19** on individuals with DS, finding that those with DS had more severe disease
- Established best practices for measuring **visual acuity** in those with DS
- Developed and validated **cognitive measures** for children with DS using the NIH Toolbox
- Developed a Behavior Inventory for Down Syndrome (BIDS) for children and adolescents with DS in English and Spanish.

INCLUDE Clinical Trials

Sleep & Apnea (OSA)

- Medications for OSA to improve cognition in children with DS
- Effects of hypoglossal nerve stimulation on cognition and language
- Positive airway pressure for OSA in children with DS
- Home Sleep Apnea Testing Compared to In-lab Polysomnography for the Evaluation of OSA in Children with DS
- Self-Supporting Nasopharyngeal Airway Treating Upper Airway Obstruction in Hypotonia
- A Personalized Surgical Approach for the Treatment of Children with Obstructive Sleep Apnea and Small Tonsils
- Treatment of Obstructive Sleep Apnea with Personalized Surgery in Children with Down syndrome (TOPS-DS)
- Randomized Controlled Trial of Oxygen Therapy in Children and Adolescents with DS and OSA

Immune System Dysregulation

- JAK inhibition for treatment of skin conditions in DS

Alzheimer's Disease & Aging

- Addition of GM-CSF/sargramostim treatment to improve cognition in DS
- The Impact of Weight Loss on Alzheimer’s Disease Risk in Adults with DS

Neurodevelopment

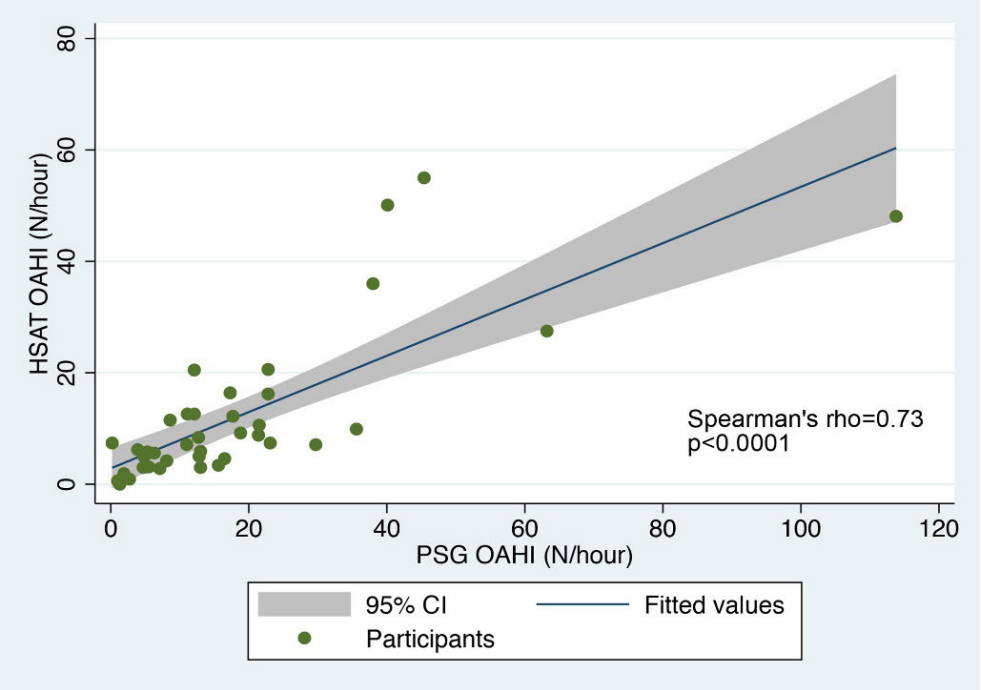
- Mechanistic investigation of therapies for Down Syndrome Regression Disorder
- Evaluating assessment and medication treatment of ADHD in children with DS

INCLUDE Clinical Trials: Promising Results

- Treatment with JAK inhibitors can reduce interferon-based inflammation
  - Potential therapeutic benefits for autoimmune and other interferon related disorders common to people with DS
  - *Galbraith, et al. PMID: 37379383 DOI: 10.1126/sciadv.adg6218*
- Combination of atomoxetine and oxybutynin (Ato-oxy) identified as a promising treatment for obstructive sleep apnea in children with DS in a randomized trial
  - *Combs, et al. PMID: 37555595 DOI: 10.5664/jcsm.10764*
- Research from the ABC-DS on amyloid and tau burden in DS presents meaningful insights into the neuropathology and progression of AD in this population
  - *Zammit MD, et al. Alzheimer's & Dementia. (2023)*

Feasibility and Performance of Home Sleep Apnea Testing in Youth with Down Syndrome

- Dearth of sleep laboratories suitable to assess obstructive sleep apnea (OSA) in youth with neurocognitive disabilities such as DS
- Tested feasibility, acceptability, and accuracy of in-home level II home sleep apnea testing (HSAT) versus polysomnography
- 43 participants (23 female) aged 6-25; 41 completed HSAT and 41 completed polysomnography; 40 underwent both tests
- Home sleep study determined to be well-tolerated, reliable, and generally preferable to hospital-based sleep studies to identify sleep apnea in individuals with DS



J. Clin. Sleep. Med. 2023 Sep 1;19(9):1605-1613. PMID: 37185265 doi: 10.5664/jcsm.10610.

What Has INCLUDE Accomplished So Far?
Data Resource Development

- Cloud-based resource developed through the **INCLUDE Data Coordinating Center (DCC)**
- Free access to large-scale data resources
- Build custom cohort datasets based on participant, biospecimen, clinical, and ‘omics data
- Encourages collaboration
- **https://includedcc.org/**
- **Coming Soon! Experimental Models of DS Researcher Portal**
  - Facilitate sharing and analysis of datasets generated from experimental models of DS, including animal models and induced pluripotent stem cells

INCLUDE Diverse Data Types

- Data from 11 studies
- More than 9,000 harmonized clinical profiles
- 4,000+ genomes
- 1,700+ transcriptomes
- 470+ proteomes
- 400+ metabolomes

- **COMING SOON!** Epigenomes, Immune Maps, Microbiomes

DS-Connect®: The Down Syndrome Registry

A secure, confidential, online survey tool to collect basic information about people with Down syndrome

Will be re-launched on a new platform hosted by the University of Colorado

~5,951 registrants globally as of January 2024

600 medical and science professionals

Promoted research enrollment in more than 100 projects

DSConnect@nih.gov

What Has INCLUDE Accomplished So Far?
Workforce Development

- More than **76 trainees and early career investigators** have benefited from INCLUDE support
  - T32 trainees
  - KL2 scholars affiliated with CTSA awards
  - Pediatric Heart Network fellows
  - Individual F31, K08, K23 awardees
  - **DS3 Data Science Scholars** program

Data Science for Diverse Scholars (DS3) in Down Syndrome Research

- **INCLUDE DCC hosts an immersive two-week summer in-person course in data science**
- Basics of generation, identification, and collection of high content multidimensional datasets; their management, analysis, and visualization; as well as the development of key professional skills required for the career advancement of diverse trainees
  - Participant travel, lodging and per diem supported
  - Available for **undergraduates, graduates, post-doctoral fellows, and early-career investigators**
- 36 trainees since 2022
- New cohort in 2025

2023 DS3 Scholars

INCLUDE Project
Summary At a Glance

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NIH IC Collaborators

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Funding Opportunities

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Clinical trials

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Data Coordination Center

76
New Trainees in the field of DS Research

13
INCLUDE Hosted Community Engagement and Outreach Events

450+
Publications

Thank you!
Questions?