



From Research to Results: How Discoveries from the Down Syndrome INCLUDE Project are Making a Difference for Families Today

Melissa Parisi, M.D., Ph.D.

On behalf of the NIH Down Syndrome Working Group

Down Syndrome Network of Montgomery County (DSNMC)

May 4, 2023





**Melissa A. Parisi,
M.D., Ph.D.**

Dr. Parisi is Chief of the Intellectual and Developmental Disabilities Branch at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH).



- The National Institutes of Health
- The INCLUDE Project
- Research projects transforming care for DS
- DS-Connect[®]: The Down Syndrome Registry



A young woman with long, dark, wavy hair is sitting in a wooden chair, smiling warmly at the camera. She is wearing a light-colored, possibly white, long-sleeved top. She is holding a dark-colored laptop or tablet in her lap. The background is slightly blurred, showing what appears to be a bookshelf or a library setting.

The National Institutes of Health

The National Institutes of Health (NIH)



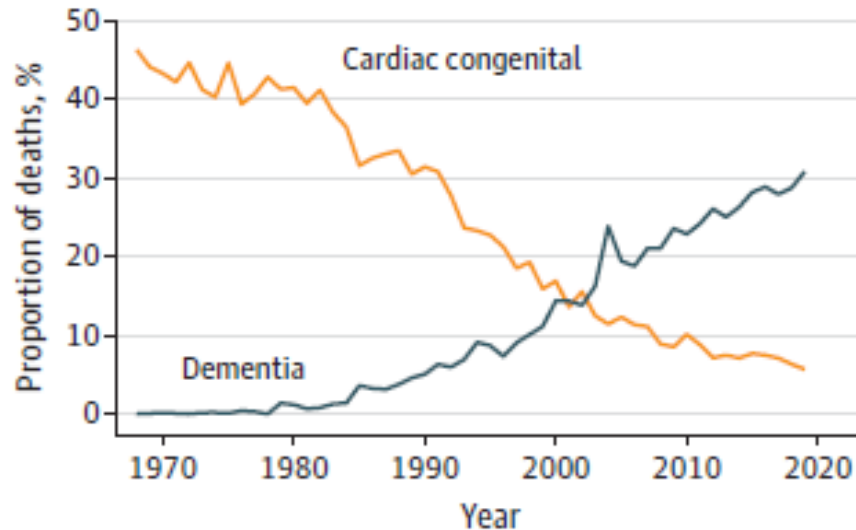
- The U.S.'s national medical research agency based in Bethesda, Maryland
- The world's largest funder of biomedical research
 - Budget: \$47 Billion for FY2023
- Made up of 27 separate research institutes and centers
- 90% of funds go to university research institutions based on peer review of grant applications



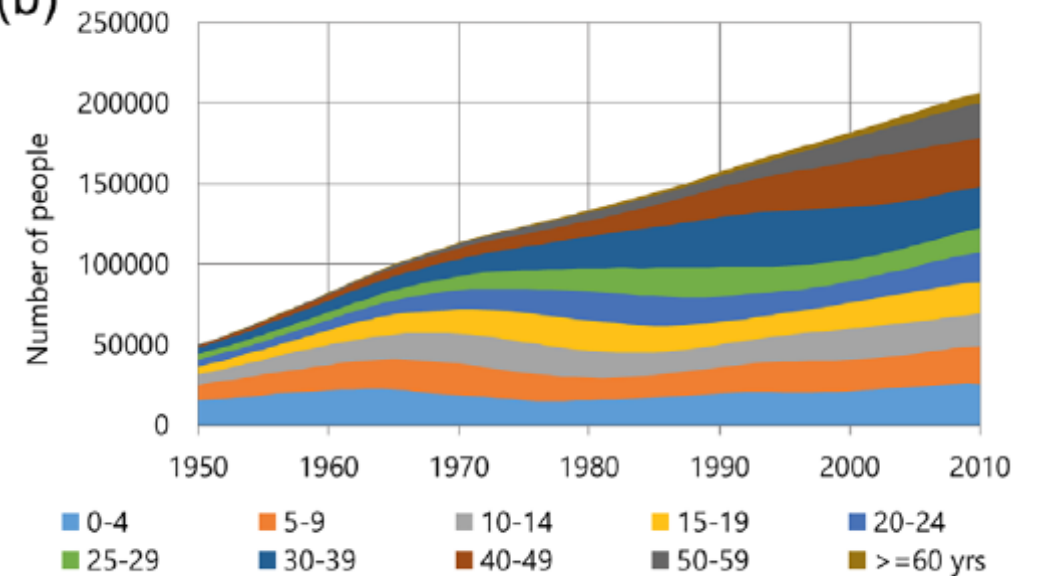


People with Down syndrome are living longer, largely due to improved medical treatments

A CDC mortality data by cause of death



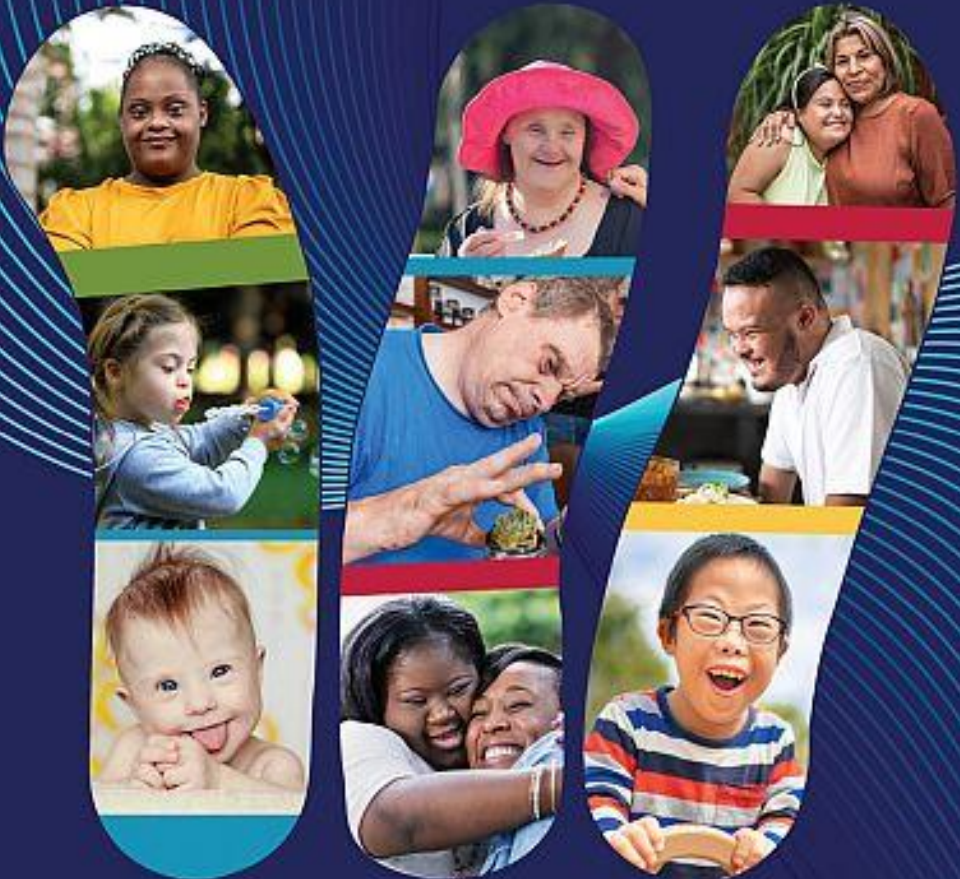
(b) Number of people with DS in the U.S. by age group, 1950-2010



- 50 years ago, congenital heart disease was the major cause of death
- Today, dementia is the leading cause of death
- In 1959, the life expectancy of a person with DS in the US was 9 years.
- The life expectancy in the U.S. is now ~ 60 years of age

New NIH Research Plan for Down Syndrome

NIH INCLUDE Down Syndrome Research Plan



- **Highlights:**
 - New Goals and Objectives reflect public input
 - Goals include increasing diversity of PIs and research participants
 - New section on Training in DS Research
 - Detailed portfolio analysis covering 2014-2020, with 592 articles listed in the bibliography
 - Findings from research on COVID-19 in individuals with DS
- **Available for download on the website:**

<https://www.nih.gov/include-project/include-project-down-syndrome-ds-research-plan>



The INCLUDE Project

nih.gov/include-project

U.S. Congressional Directive

- Launched in 2018 under a Congressional Directive to address **critical health and quality of life needs for those with DS.**
- INCLUDE is investigating **conditions** that affect individuals with DS and the general population, such as Alzheimer's disease, autism, cataracts, celiac disease, congenital heart disease, and diabetes.
- The project will also **increase the number of investigators/trainees** studying DS.
- The project will engage with those with DS and their families from **diverse backgrounds.**

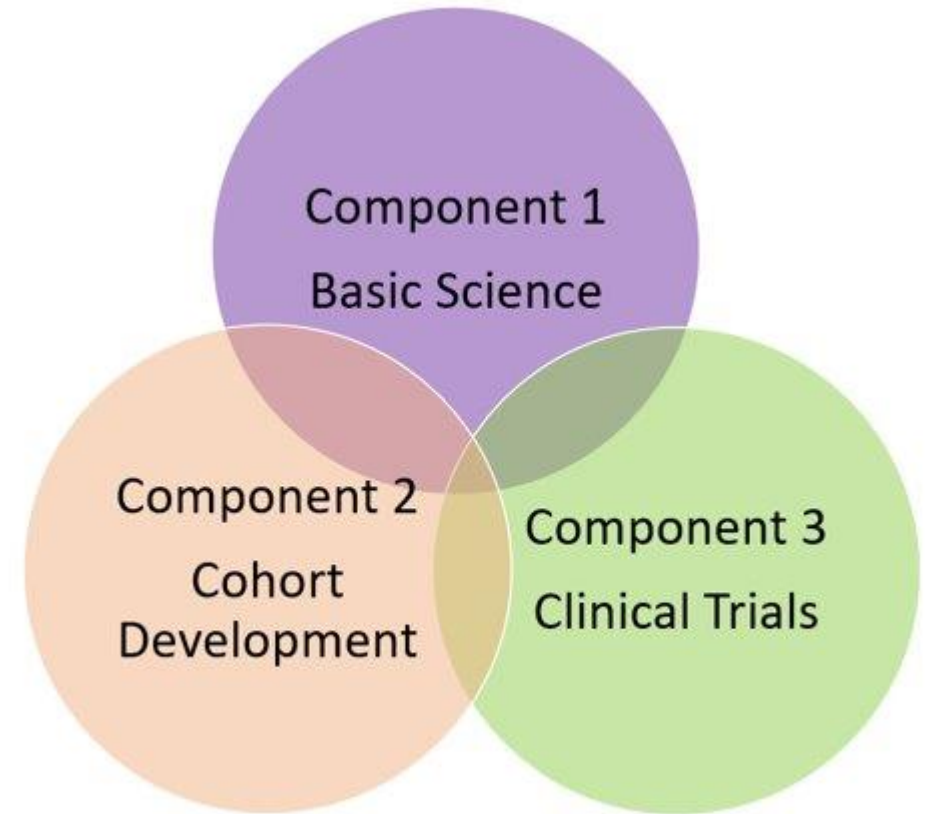




INCLUDE (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE)

3 components:

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**.



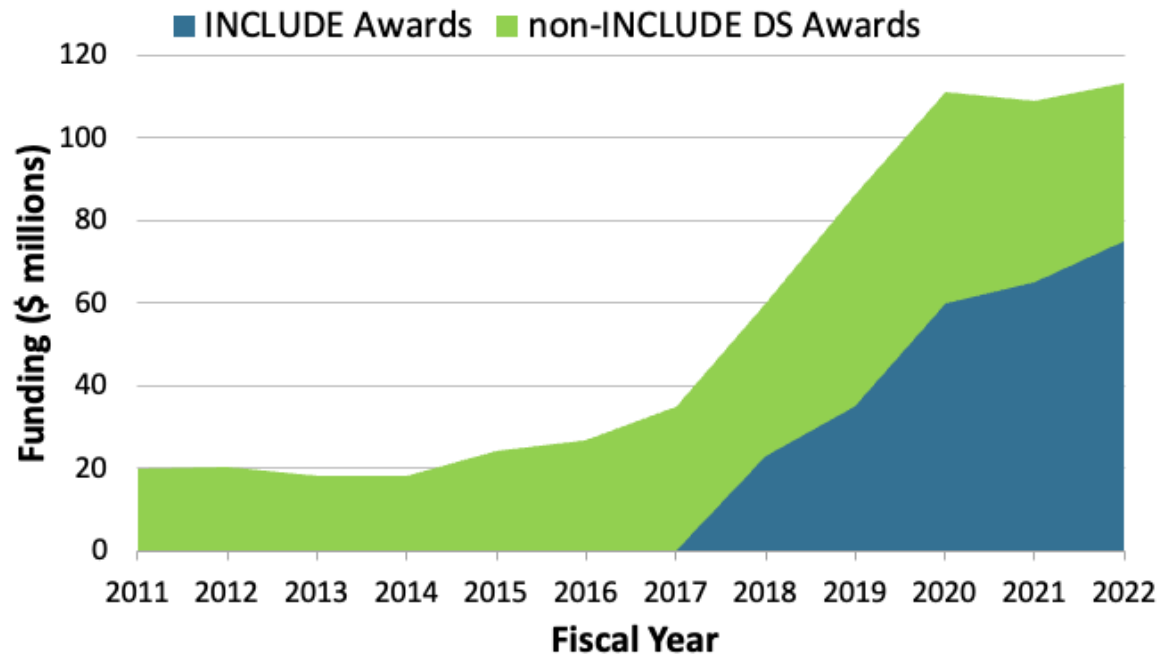
URL: <https://www.nih.gov/include-project>

Down Syndrome Funding at NIH



FY2011-FY2022

nih.gov/include-project



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*

The NIH has invested **\$258 million** in the past **5 years** on **270** new projects for **INCLUDE**

*non-INCLUDE totals for FY22 are estimated and will be finalized in early 2023



**Research projects
transforming care for DS**



What has **INCLUDE** done so far?

- Investigate the **impact of COVID-19** on individuals with DS.
- Study the causes of **acute lymphoblastic leukemia** in children with DS
- Develop and validate **cognitive measures** in the NIH Toolbox for children with DS.
- Study **language acquisition and articulation** in children with DS
- Study the causes of **congenital heart disease** in infants with DS, and whether heart surgery impacts their neurodevelopment and behavior
- Study a cohort of adults with DS to identify **biomarkers of neurodegeneration** and risk and resilience factors for Alzheimer's disease



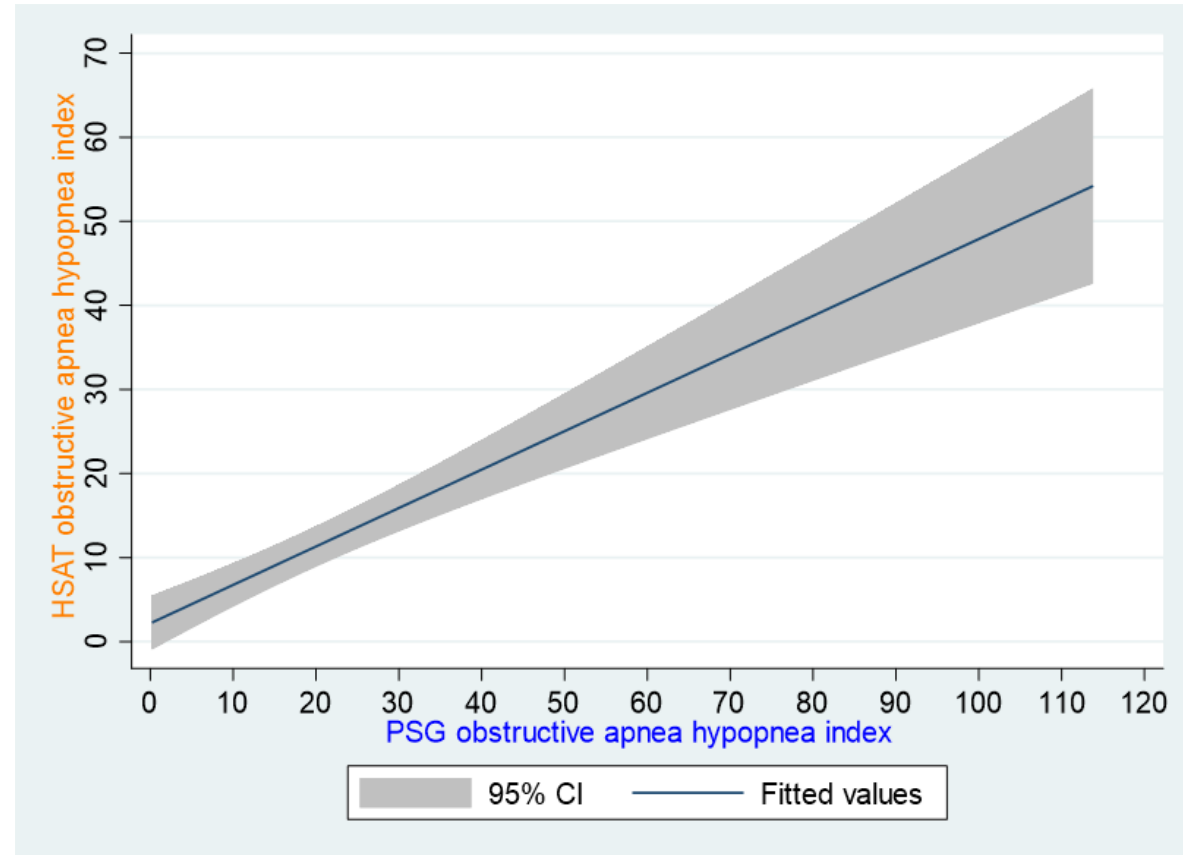
Sleep apnea in Down syndrome

- Sleep apnea: breathing difficulty during sleep that reduces oxygen levels and cause frequent waking
- Obstructive sleep apnea (OSA) occurs when airway is blocked
- ~53-76% of children with DS have sleep apnea (vs. 1-4% in those without DS)
- Causes of OSA:
 - Facial structure—narrow airway in nose and throat
 - Low muscle tone
 - Poor coordination of airway movements
 - Large adenoids, tonsils, and tongue
 - Frequent respiratory infections and reflux
- Consequences:
 - Irritability, tantrums, behavior and learning problems
 - Increased risk of heart disease, pulmonary hypertension

Home Sleep studies



- Dr. Ignacio Tapia: Improving Sleep for those with Down syndrome
- Sleep apnea is common in Down syndrome
 - If not treated, can lead to worse cognitive function and hypertension
- But in-hospital sleep studies (PSG) are not well tolerated
- Need for Home Sleep studies (HSAT)



Sleep in Down syndrome: making PAP easier to tolerate

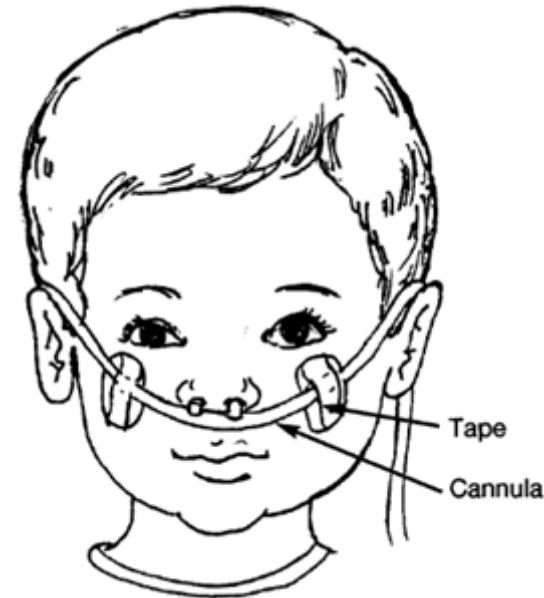
- Once sleep apnea has been diagnosed in children with Down syndrome...
- Removing tonsils and adenoids doesn't always correct the problem
- Positive Airway Pressure (PAP) is one treatment method
- Developing strategies to increase PAP use





Randomized Control Trial of oxygen therapy in Children and Adolescents with Down Syndrome and Obstructive Sleep Apnea

- Another strategy to treat sleep apnea
- 6-month randomized, controlled trial of oxygen supplementation during sleep
- Outcome on neurocognitive, cardiac, quality of life and sleep measures
- Plan to recruit 328, 5-17 yrs. old children with DS from 6 sites

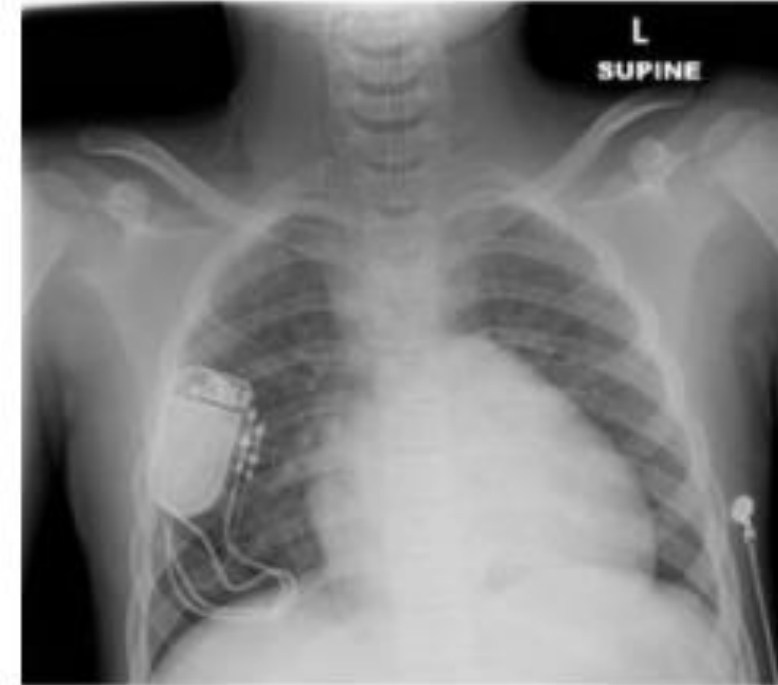


PI: Dr. Susan Redline



Effects of Hypoglossal Nerve Stimulation (HGS) on Cognition & Language in Down Syndrome

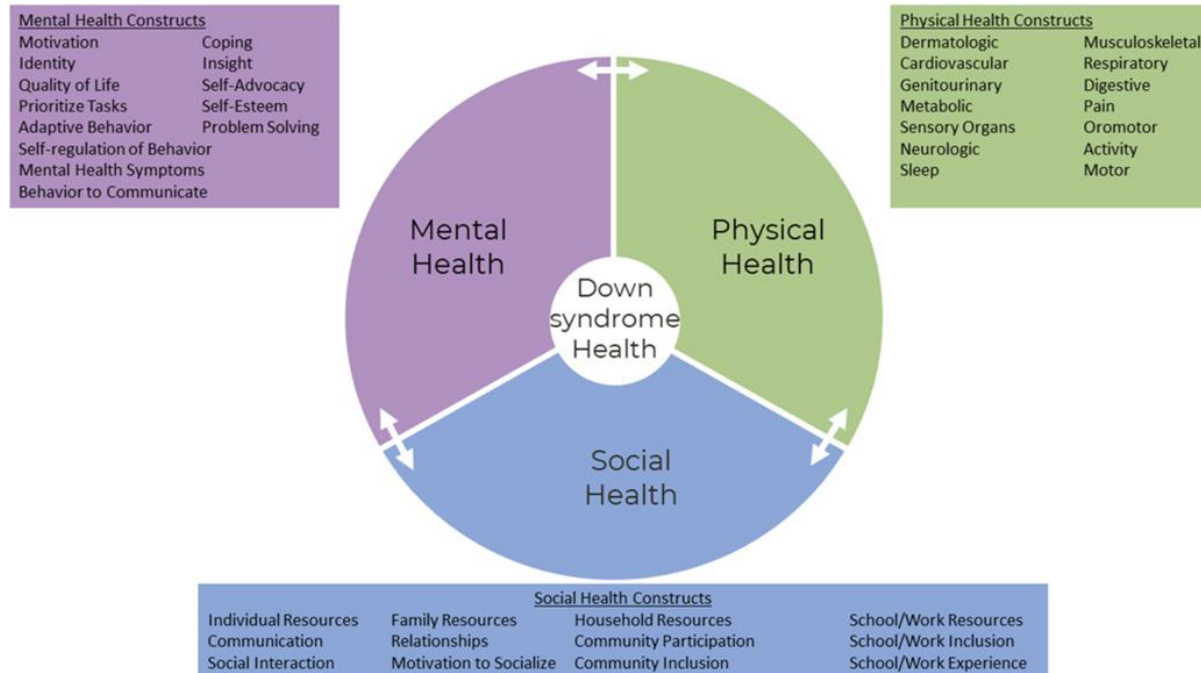
- Obstructive sleep apnea (OSA) may be linked to severe impairments in speech and language
- HGS is a novel therapy for OSA in adults and children with DS
- The primary outcome is implant safety
- Secondary measures are changes in the standard measure of OSA called the Apnea-Hypopnea Index
- This proposed study focuses on the effects on neurocognition and expressive language before and after HGS treatment for OSA
- Recruiting 57 children and adolescents (10 to 21 years of age)



Source: Statnews.com

Pis: Dr. Christopher Hartnick and Dr. Brian Skotko

Down Syndrome Health Instrument



- Career Development Grant
- Validated instrument for measuring health status of individuals with DS (DHI)
- Focus groups (caregivers, individuals with DS, panels of experts on DS and primary care physicians)
- Administering and validating the DHI in clinical research
- **SL Santoro et al, Journal of Intellectual Disability Research, Volume 67, April 2023**

PI: Dr. Stephanie Santoro



TEAM-DS: Treatment Efficacy and safety of ADHD Medication in Down Syndrome

- Clinical trial of stimulant medication (Methylphenidate) in children with DS+ADHD
 - Initial studies: define ADHD in DS
 - To determine the short- and long-term efficacy and safety of these medications
 - Improve the functional status, behavior, and quality of life of children with DS and ADHD
- Adding additional sites to increase enrollment—4 sites total:
 - Cincinnati, UC Davis, Pittsburgh, Boston



PI: Dr. Anna Esbensen; Dr. Tanya Froehlich

Source: UC Davis study site



Neurobehavioral Research on Infants at Risk for Language Delay and Autism Spectrum Disorder (ASD)

- ~15-20% of those with DS have autism
- Early developmental delays:
Communication disorders
- Identify ASD in DS in the first year of life
- Using brain imaging tools (EEG)
- Behavioral data and Ages and Stages
Questionnaire to predict risk for ASD in DS
- Focusing on language and social
communication development



Pic credit: The LonDowns Consortium website

PI: Dr. Helen Tager-Flusberg; Dr. Charles Nelson



Treatment of autoimmune skin disorders

- Dr. Joaquin Espinosa: JAK inhibitor to treat 5 autoimmune skin conditions
- Autoimmune conditions are more common in Down syndrome: Celiac disease, diabetes, thyroid, alopecia (hair loss)
- Can an FDA-approved drug, Tofacitinib, treat skin autoimmune conditions in DS?



Baseline
SALT = 86

17-year-old male
with
alopecia
areata

Week 16
SALT = 4

Participant known to the research team as 'Ed Sheeran'



Significant improvement in one measure of visuomotor function

The NEPSY II test

Participants are asked to 'track' the path with a pencil

The task is videorecorded and analyzed for errors and time to completion

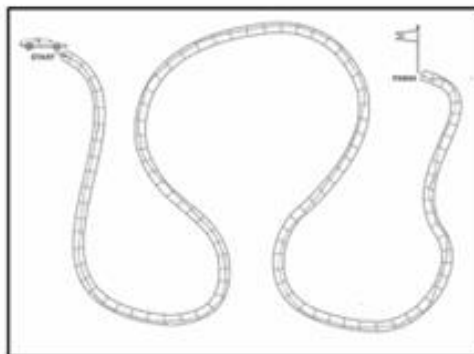
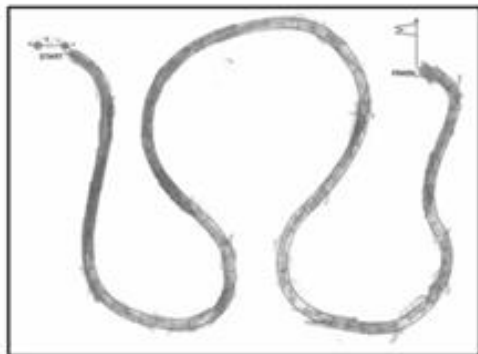
Result: significant decrease in the total number of errors

NEPSY II (car)

NEPSY II (motorcycle)

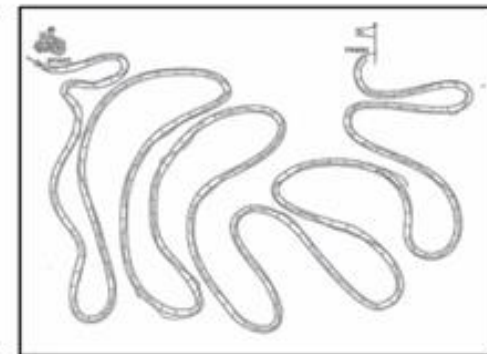
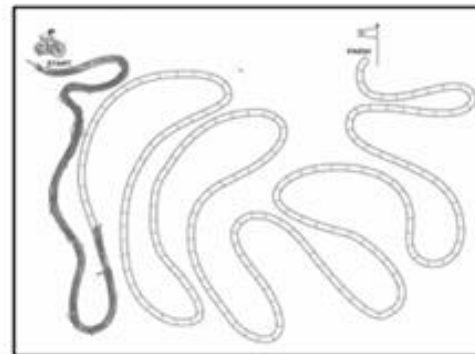
Baseline

Week 16



Baseline

Week 16



Alzheimer's Disease in DS



Many people with DS begin to show signs of Alzheimer's disease (AD) in their 50s and 60s

- Alzheimer's Biomarkers Consortium of Down Syndrome (ABC-DS):
 - Funded by NIH, now in 8th year: ~\$105 M over 5 years
 - > 400 adults with Down syndrome, plus healthy sibling controls
 - Age >25 years
 - Studies of biomarkers that may help diagnose Alzheimer's before symptoms appear:
 - Cognitive tests
 - Genetic studies
 - Brain scans (amyloid, tau)
 - Blood biomarkers
 - nia.nih.gov/research/abc-ds
- **INCLUDE** projects to understand aging in DS
 - Lifestyle risk and resiliency factors and Alzheimer's disease in DS
 - Clinical trial to test preventive treatments for dementia in adults with DS
 - GM-CSF treatment to improve cognition in Down syndrome

13 Clinical Trials Funded by INCLUDE

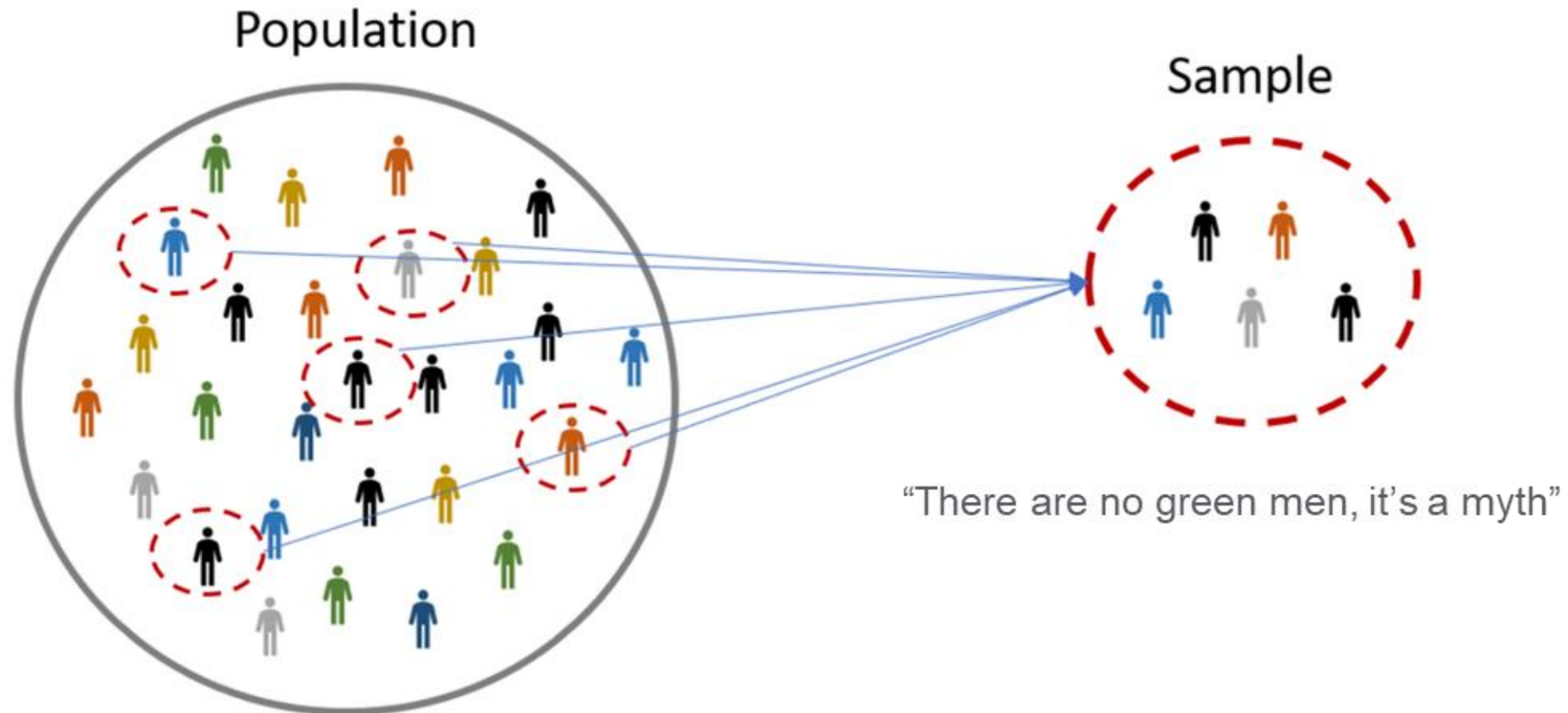
- Sleep & Apnea (OSA)
 - Medications for OSA to improve cognition in children with DS*
 - Effects of hypoglossal nerve stimulation on cognition and language in DS
 - Positive airway pressure for OSA in children with DS*
 - Home Sleep Apnea Testing Compared to In-lab Polysomnography for the Evaluation 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
 - Randomized Controlled Trial of Oxygen Therapy in Children and Adolescents with DS and OSA
- AD & Aging
 - Clinical trials to prevent Alzheimer's Disease in DS*
 - 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
- Immune System Dysregulation
 - JAK inhibition for treatment of DS skin conditions*
- Neurodevelopment
 - Mechanistic investigation of therapies for Down Syndrome Regression Disorder
 - Evaluating assessment and medication treatment of ADHD in children with DS*

* Awarded in FY19, now transitioned from R61 to R33 phase

The importance of sample size for research



By harmonizing and aggregating data from different cohorts, we can enlarge the 'sample size' and enable new discoveries



"14% of men are green"





INCLUDE
Data Coordinating Center

IncludeDCC.org

Improving the quality of life of people with Down syndrome

The INCLUDE Data Coordinating Center (DCC) is making it easier for scientists and the Down syndrome community to work together. Matching the latest technology with shareable resources, we are building a system to improve healthcare and change lives.

[Learn more →](#)

[Contact Us](#)



INCLUDE DCC Cores

DATA PORTAL CORE



Facilitate access to and analysis of data via web portal

DATA MANAGEMENT CORE



Manage data collection, processing and harmonization

ADMINISTRATIVE & OUTREACH CORE



Provide program management, outreach, education and support



- Quarterly webinar series on topics about clinical trials with participants with DS
- First webinar held on November 15th: Assent and Consent
- Second webinar on April 25th: Let's Talk about Clinical Trials
 - Overview on Types of Clinical Trials
 - Reasons to Get Involved
 - Role of Family, Caregiver
 - Perspectives from a Self-Advocate and Family Member
 - Audience: General Public
- Videocast is available for viewing: <https://videocast.nih.gov/watch=49451>

NIH National Institutes of Health
INCLUDE Project Clinical Trials Seminar:
Let's Talk About Clinical Trials
 Lauren Ptomey, PhD, RD, LD Shawn Robert Kortan Lisa M. Kortan
 April 25, 2023
 1:00 pm - 2:00 pm ET
 Register today at:
www.cvent.com/d/q0q0fk

INCLUDE Diversity Activities



**Building a Diverse Community
for Down Syndrome Research**

Virtual Workshop
September 20–21, 2022

NIH National Institutes of Health

Meeting Overview

- Engaging the DS Community
- Expanding Diversity of DS Participants
- Increasing Diversity of DS Researchers/Trainees

Key Features

- Built on May 2022 listening sessions
- Simultaneous Spanish interpretation
- 38 speakers and 300+ attendees from >10 countries
 - COSWD, NINDS Neuroscience Workforce Diversity office, CTSA Recruitment Innovation Center (RIC)
 - Diverse panel representation: Honoraria for participating family members and self-advocates

Next Steps

- **DEIA Webinar Series starting June 26, 2023, 1-3 PM ET**
- **Focused outreach to underrepresented DS groups**

DS-Connect® The DS Registry

DSConnect.nih.gov





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



The screenshot shows the DS-Connect website homepage. At the top, there is a navigation bar with links for LOGIN, JOIN, and NEED HELP?, along with US and Spanish flags. Below this is the NIH logo and the text "National Institutes of Health Turning Discovery Into Health". A secondary navigation bar includes links for Home, About DS-Connect®, News, Resources, Research, Glossary, For Professionals, and Contact Us. The main content area features a large photograph of a woman with Down syndrome smiling and being embraced by another woman. Below the photo, the text reads: "DS-Connect® is a powerful resource where people with Down syndrome and their families can:" followed by a bulleted list of benefits. At the bottom, there are three buttons: "Join the Registry", "Set up a Professional Account", and "Información en español". A blue arrow points from the "Información en español" button to a yellow box on the right that says "Available in Spanish".

NIH National Institutes of Health
Turning Discovery Into Health

Forgot login?
Unblock Account

Home | About DS-Connect® | News | Resources | Research | Glossary | For Professionals | Contact Us

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 certain clinical studies on Down Syndrome, including studies of new medications and other treatments.
- Take confidential health-related surveys. These surveys are aimed at better understanding of the health of people with Down Syndrome across their lifespans.

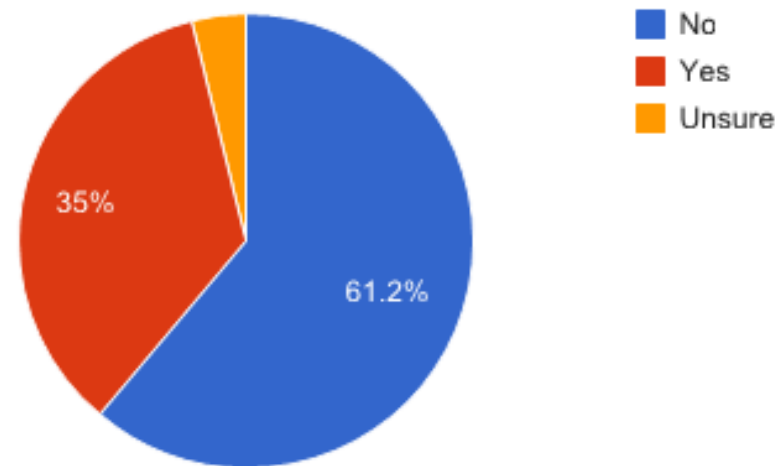
Join the Registry | Set up a Professional Account | Información en español

Available
in
Spanish

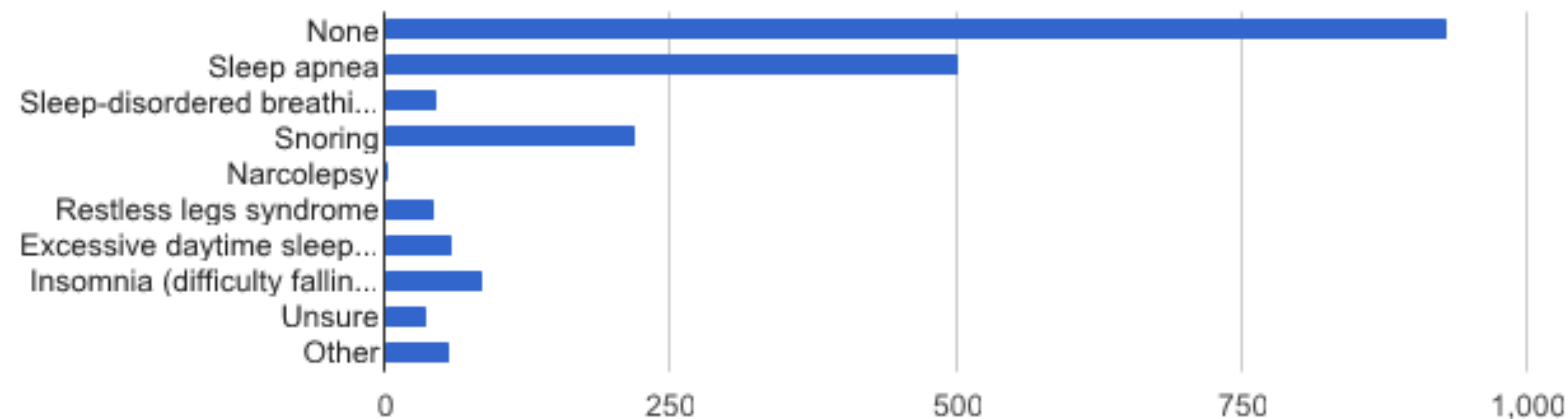


Has the participant ever been diagnosed with any sleep problems? (1803 responses)

Example: Sleep



Which of the following sleep problems problems have been diagnosed? (Select all that apply.)





Access the healthcare provider list

Questionnaire **Healthcare Providers** Growth Measurements Account Info Attachments Contacts Newsletters

Notes

Search the directory for your health care provider(s) by name, facility name, city or state (2 letter abbreviation). If your health care provider is not in the directory, use the Add a New Health Care Provider link to add them in the directory. Note that you will need to search for each physician individually before the Save button will be enabled.

Please note that this list of healthcare providers does not imply endorsement or recommendation of their services.

Name/Institution Specialty City State

Country

Search

Leave blank to list all

[Add a New Health Care Provider](#) Click the to add the healthcare provider to your account.

Name	Specialty	Sees Adults or Youth?	Institution	City	State	Country	
John Avallone	Ophthalmology		Ophthalmology Associates	Arnold	MD	UNITED STATES	My Health Care Provider
Mihee Bay	Developmental Pediatrics		Kennedy Krieger Institute	Baltimore	MD	UNITED STATES	My Health Care Provider

~864 now Listed!



Access the healthcare recommendations

- Personalized for the age of the person with DS

Health Care Guidelines for Individuals with Down Syndrome

Children with Down Syndrome: Health Care Information for Families (AAP)

Global Medical Care Guidelines for Adults with Down Syndrome (GLOBAL)

Aging and Down Syndrome: A Health & Well-Being Guidebook (NDSS)

Alzheimer's Disease & Down Syndrome: A Practical Guidebook for Caregivers (NDSS)

Links to AAP checklists

Health Care Information for Families of Children with Down Syndrome

Child's Age: 13 to 21 Years or Older

Regular well-care visits (check-ups)

It is important to have yearly well-care check-ups. These visits will assist in checking your child's health, giving shots, and answering questions about your child's health.

Monitor growth

It is important to check growth at every visit. Measurements include height, weight, and body mass index (BMI). These measurements are very important to assessing the overall health of the child. Discuss diet, activity level, and growth. Your child's doctor can help with question about any need for vitamins or supplements.

Links to the GLOBAL Medical Care Guidelines for Adults with Down Syndrome



Links to the NDSS guidebooks





[Home](#) | [About DS-Connect®](#) | [News](#) | [Resources](#) | [Research](#) | [Glossary](#) | [For Professionals](#) | [Contact Us](#) | [Clinical Trials](#)

Find Down Syndrome Clinical Trials

Search for NIH-funded clinical trials related to Down Syndrome

Filter by:

Location:

Age

[Search](#)

[Clear](#)

[See all NIH-funded Down Syndrome clinical trials](#) 

To search all clinical trials, visit clinicaltrials.gov



Join the Registry

Set up a Professional Account

Información en español



A transcript of the video is available at <https://dsconnect.nih.gov/video-text-alternative.html>
[How do I turn on subtitles/captions and specify their language?](#)

In the last 7 years:

- 100 studies have requested recruitment support
- Over 90% were approved by the Research Review Committee
- 15 INCLUDE projects have received recruitment support, including 5 clinical trials

532 Researchers Registered

What is a research study?—it's your choice!



- Take a survey of your experiences
- Answer a questionnaire about health issues
- Record data from an activity tracker (e.g., Fitbit)
- Participate in a clinical study of an intervention
- Be in a clinical trial for a new drug or medication
- Participate in an INCLUDE study
- Any of the above! It's your choice**



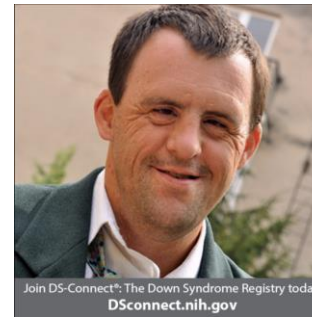
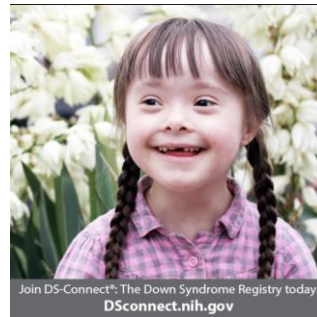
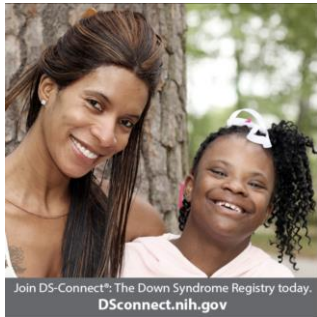


Help us reach our goal:

- **10,000** by September 2023, the 10-year anniversary of DS-Connect

Electronic Toolkit available:

- Info-Cards
- Flyers in English and Spanish
- Post [free, pre-made messages and graphics](#) on social media and in emails.



Engagement with the DS Community:

- Outreach to DS advocacy groups, community members, researchers, clinicians
- Contact us for links to our materials or for flyers for your events: DSConnect@nih.gov



INCLUDE Project and DS-Connect

- Respect the rights of persons with DS, using “people-first” language
- Share data broadly and rapidly
- Increase the diversity of researchers and participants
- Outreach to families is essential to its success
- Partner with advocacy groups

Research can benefit everyone



Thank you!



Acknowledgements



- The NIH-wide Down Syndrome INCLUDE Working Group
- NIH Staff who support the INCLUDE Project
- **Investigators**
- **Children and adults with Down syndrome and their families**

The Down Syndrome Consortium



[National Cancer Institute \(NCI\)](#)

[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 \(NIAID\)](#)

[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 Mental Health \(NIMH\)](#)

[National Institute on Minority Health and Health Disparities \(NIMHD\)](#)

[National Institute of Neurological Disorders and Stroke \(NINDS\)](#)

[National Center for Advancing Translational Sciences \(NCATS\)](#)



DOWN SYNDROME AFFILIATES IN ACTION



Self-Advocates

