

Title: First Three Years of a Down Syndrome-Focused Research Program: Updates on the INCLUDE Project

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Background: The [INCLUDE](#) (Investigation of Co-occurring conditions across the Lifespan to Understand Down syndrome) project was launched in June 2018 in support of a Congressional directive in the fiscal year (FY) 2018 Omnibus Appropriations legislation. The directive called for a new trans-NIH (National Institutes of Health) research initiative on critical health and quality-of-life needs for individuals with Down syndrome (DS). In 2018, NIH dedicated almost \$23 million under this new project through administrative supplements, and about \$35 million in grants in FY 2019. NIH recently announced about \$60 million in new grants in FY 2020 through the INCLUDE project, including 7 COVID-19 related supplements. This initiative, involving multiple NIH Institutes and Centers (ICs), aims to include people with DS in all aspects of research, from support for dedicated basic science studies through opportunities to participate in existing clinical trials. In addition, NIH recently sponsored a workshop to promote clinical trials in DS and is hosting a workshop in November 2020 to connect basic scientists and cohort developers. INCLUDE will investigate conditions that affect individuals with DS and the general population, such as intellectual disability, Alzheimer's disease/dementia, autism, cataracts, celiac disease, congenital heart disease, diabetes, and COVID-19.

Project: Applying the expertise and resources from multiple NIH ICs, INCLUDE will:

- 1. 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.
- 2. Assemble a large study population of individuals with Down syndrome.**
 - Add to or expand existing DS cohorts with 'omics data.
 - Develop shared databases using common data elements.
 - Employ the DS-Connect® registry (<https://DSConnect.nih.gov>) to connect families with research opportunities of interest to them.
- 3. Include individuals with Down syndrome 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 NICHD's existing clinical trials infrastructure to explore drug metabolism in those with DS and provide assistance and training in clinical trial design in order to inform future clinical trials.

Funded Proposals: The FY 2020 awards bolster total NIH funding for DS research in FY 2020 to ~ \$113 million. Research will:

- Investigate the impact of COVID-19 on individuals with DS.
- Create a Data Coordinating Center to support investigations of a large cohort of people with DS for data sharing, data access, and integrative analysis.
- Use murine and cell-based models to explore the expression of certain genes on chromosome 21.
- Test if deficits in cellular recycling lead to increased susceptibility to leukemia and other conditions in those with DS.
- Explore the neuropathology, vascular changes, and memory loss in mouse models of DS.
- Develop and validate cognitive measures in the NIH Toolbox for children with DS.
- Identify domains of very early cognitive and motor decline in young adults with DS.
- Continue to follow a cohort of adults with DS to identify biomarkers of neurodegeneration and risk and resilience factors that modify the development of Alzheimer's disease in the Down syndrome population.

Conclusions: DS is associated with intellectual and physical challenges resulting from the presence of extra genetic material from chromosome 21. Individuals with DS experience various rates of cognitive disability and in later years, dementia resembling Alzheimer's disease, as well as hearing loss, congenital heart defects, and sleep apnea. Autism and epilepsy are prevalent in the population, as are autoimmune disorders such as celiac disease. However, individuals with DS infrequently develop solid tumors, such as breast or prostate cancer, or have heart attacks despite having multiple risk factors, such as obesity and type 1 diabetes. Research funded by INCLUDE will investigate critical health and quality-of-life needs for individuals with DS who may have these co-occurring conditions; this information will also benefit individuals who do not have DS but may have the same conditions.

References: N/A