

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 is investigating 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.

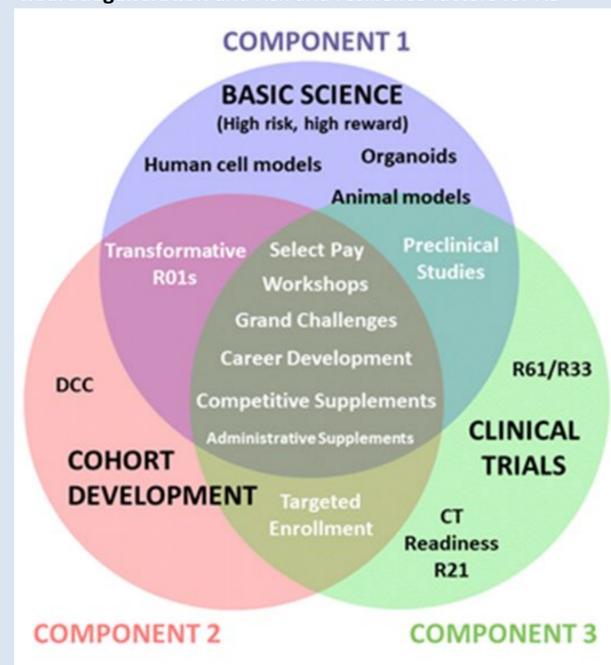
INCLUDE Project Objectives

- 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 across the lifespan.**
 - Add to or expand existing DS cohorts with 'omics data
 - Develop shared databases using common data elements
 - Build on the DS-Connect® registry to connect with families with research opportunities of interest to them.
- 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.

FY2020 Funded Projects

The NIH has invested \$118 million in the past 3 years on INCLUDE and plans to spend \$65 million in FY2021. **The FY 2020 awards bolster total NIH funding for DS research in FY 2020 to ~ \$109 million. Research will:**

- Investigate the **impact of COVID-19** on individuals with DS.
- Study the molecular epidemiology of **acute lymphoblastic leukemia** in children with Down syndrome
- Develop and validate **cognitive measures** in the NIH Toolbox for children with DS.
- Study the effects of **hypoglossal nerve stimulation** on language and cognition
- Study a cohort of adults with DS to identify **biomarkers of neurodegeneration** and risk and resilience factors for AD



INCLUDE DCC Goals:

- To engage and empower a **diverse community of stakeholders** via the INCLUDE DCC to drive collaborative, accelerated discovery.
- To create an integrated **data ecosystem** that will foster innovation, collaboration, and transformative discoveries.
- To empower the community with **resources for data access, data discoverability, and collaborative analysis tools** required for transformative action and impact from bench to bedside.

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 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.

In the past 5 years:

- 60 studies have requested recruitment support*
- Over 90% were approved by the RRC
- 10 INCLUDE projects have received recruitment support, including 5 clinical trials

*Requires submission of a summary of protocol, purpose and IRB Status and review by the Research Review Committee (RRC) for approval

Current Funding Opportunities

The following FOAs have due dates in FY21 and FY22:

Four RFAs published in FY20:

- Transformative high-risk, high-reward basic science (R01) ([RFA-OD-20-005](#))
- Clinical trial readiness (R21) ([RFA-OD-20-004](#))
- Treatment trials (Phased awards: R61/R33) ([RFA-OD-20-003](#))
- Data Analysis and Secondary Data Analysis (R03) ([RFA-OD-20-006](#))

Eight new notices published in FY20:

- 3 NOSIs for fellowship and career development awards
- 1 NOSI to develop animal models of DS
- 1 NOSI for R01s for DS
- 2 NOSIs for supplements
- 1 NOSI for supplements for SARS-CoV-2

Several new FOAs under development in FY21

Down Syndrome Research Plan

NIH is updating the DS research plan, combining it with the INCLUDE research plan, to reflect broad stakeholder input into its revised goals and objectives. NIH issued two **Requests for Information** inviting the public to provide input on the 2021 Draft NIH INCLUDE Down Syndrome Research Plan. Responses are being included in the revised plan, scheduled to be published in late summer 2021.

CONCLUSIONS

- The new trans-NIH INCLUDE initiative is making major investments in DS research, in basic science, cohort development, and clinical trials domains
- The newly funded INCLUDE Data Coordinating Center aims to accelerate discovery in DS research by integrating data sets and facilitating data analysis and collaboration
- DS-Connect® is an online registry that facilitates recruitment of families to research studies
- Engagement from the DS community, including DSMIG membership, is essential to inform these efforts and encourage broad representation in research to improve quality-of-life for those with DS

Down Syndrome Consortium

