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

Authors: Rachel Goldman, Sujata Bardhan, Lisa Kaeser, Melissa Parisi, and the NIH Down Syndrome Working Group

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. NIH recently announced about $35 million in new grants in FY 2019 through the INCLUDE project. 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 explore strategies for assembling a virtual DS cohort across the lifespan from existing and prospective studies. INCLUDE will investigate conditions that affect individuals with DS and the general population, such as Alzheimer’s disease/dementia, autism, cataracts, celiac disease, congenital heart disease, and diabetes.

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.
   - Build on 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 under INCLUDE.

Funded Proposals: The FY 2019 awards bolster total NIH funding for DS research in FY 2019 to ~ $77 million. Research will:

- Study gene silencing to understand functions of genes on chromosome 21, particularly in brain development.
- Investigate immune dysregulation in DS, which may explain the unique tumor spectrum found in individuals with DS.
- Expand the Pediatric Cardiac Genomics Consortium for uncovering causes of congenital heart defects in those with DS.
- Develop customized and improved cognitive and neurodevelopmental outcome measures in a cohort of young adults with DS, thus paving the way for meaningful clinical trials for these individuals.
- Launch clinical studies to understand and protect against the unique cardiotoxicity observed in children with DS undergoing treatment for acute lymphoblastic leukemia.
- Build a ‘trial-ready’ cohort of adults with DS and conduct a trial of an anti-amyloid therapeutic agent for Alzheimer’s disease tailored for these individuals.
- Explore options for home-based evaluation for obstructive sleep apnea and conduct clinical trials to address sleep apnea outcomes in children with DS.

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