

**Down Syndrome Research:  
The Intersection of Basic Science and Clinical Cohort Development**  
November 9–10, 2020  
NIH-Sponsored Virtual Meeting<sup>1</sup>

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## EXECUTIVE SUMMARY

On November 9–10, 2020, the National Institutes of Health (NIH) in Bethesda, MD, sponsored a virtual workshop of [the INCLUDE Project](#) (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE) titled “Down Syndrome Research: The Intersection of Basic Science and Clinical Cohort Development.” Representatives from NIH, basic and clinical researchers, self-advocates, and other members of the Down syndrome (DS) community participated in the 2-day meeting and gave presentations on the current state of the science and gaps with regard to basic research and cohort development. Meeting attendees also participated in a series of topic-driven sessions to discuss these issues and identify priorities for further research and development.

The 2-day meeting was co-hosted by Melissa Parisi, M.D., Ph.D., who oversees the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Intellectual and Developmental Disabilities Research Centers, and Charlene Schramm, Ph.D., program officer, National Heart, Lung, and Blood Institute (NHLBI).

Day 1 included an overview of the INCLUDE program, current INCLUDE funding opportunities and INCLUDE projects funded over the past 3 years, keynote presentations, and reports from pre-meeting topical working groups and topic-driven breakout sessions. Day 2 opened with two concurrent sessions, one to discuss basic science and the other to discuss cohort development; continued with a second series of breakout groups; and closed with a panel of experts from the DS research community to discuss what basic scientists and clinical investigators want each other to know. More than 300 people registered to attend the workshop.

### INCLUDE Overview and Funding

The INCLUDE Project was launched in June 2018 and supports a broad range of research to address critical health and quality-of-life needs for people with DS. It is a trans-NIH program involving 18 NIH Institutes and Centers (ICs). The three goals of INCLUDE are to:

- Conduct targeted, high-risk, high-reward basic science studies on chromosome 21
- Assemble a large study population of people with DS across the lifespan
- Include people with DS in existing and future clinical trials

The workshop focused on the first two components of INCLUDE.

Initial funding for INCLUDE was awarded in the second half of fiscal year (FY) 2018, at a level of \$24 million supporting 49 supplemental awards. Funding has increased steadily each year since. In FY 2019, \$35 million was distributed among 43 awards. In FY 2020, the total amount of INCLUDE funding increased to \$60 million supporting a total of 63 awards, of which 42 were new. NIH anticipates that this level of support will be maintained through FY 2022. Each year, projects have been funded in all three components of INCLUDE. Since 2019, the program also has supported a total of 24 new trainees, from predoctoral candidates to postdoctoral fellows to M.D. and Ph.D. scholars.

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<sup>1</sup> All presentations from [Day 1](#) and selected presentations from [Day 2](#) will be accessible on the [NIH VideoCast](#) site.

## **Keynote Presentations: Perspectives from Research Study Participants**

Day 1 of the meeting included keynote presentations by two young people with DS and their families who have participated in clinical studies of DS. The presenters offered their personal views on the importance of engaging with participants throughout the course of the clinical trial, making the experience personal and relevant, and sharing the outcomes of the study. In addition, they said their research experience gave them a familiarity with hospitals and health providers, which made going to see the doctor a more positive experience. They asked that investigators try to schedule invasive research procedures such as blood draws to coincide with the participants' routine health care visits. The advocates emphasized the need to keep study participants informed about research updates using social media and understandable language and educate and engage potential candidates about clinical trials. They suggested that more information about the transition from adolescence to young adulthood is needed.

## **Day 1 Reports from Working Groups and Breakout Sessions**

Presentations on co-morbidities associated with DS followed the keynote presentations, with discussions on neurodevelopment, behavior, cardiovascular disease and pulmonary hypertension, and respiratory and airway conditions. Additional presentations were given on cancer; autoimmunity and infections; endocrine, metabolic, and skeletal conditions; and aging and Alzheimer's disease (AD). The meeting then divided into Breakout Groups 1 (Development and Behavior), 2 (Heart and Lung), 3 (Cancer and Immunity), and 4 (Aging and Metabolic Conditions). The breakout groups identified some common themes, including the need for longitudinal cohort studies with well-validated endpoints, better animal and cellular models for preclinical data, more cohort diversity, integration of adult and pediatric cohorts into a single cohort across the lifespan, collection of "samples of convenience" from routine surgical procedures, and better harmonization and linkage of databases. On the basic science side, the breakout groups discussed the need to bring together information on phenotypes of various mouse models, provide more funding opportunities for model development, and develop induced stem cells to generate lines from people with DS. It was announced during Day 1 of the meeting that whole genome sequencing data on 2,600 people with DS would soon be available to be shared with the community.

## **Day 2 Session on Basic Science: Model Systems and Tools to Advance Down Syndrome Basic and Preclinical Science**

This session focused on the current state of DS mouse models. An overarching issue was the importance of knowing the background of the mouse model used in research studies because many factors can affect the mouse phenotype, such as the strain of the mouse and how the model was derived. One promising model is the TcMAC21 mouse, which has an artificial chromosome containing the long arm of human chromosome 21, retains 93% of the human chromosome protein coding genes, and is not mosaic. Work has also begun to put the human chromosome 21 in rats, which tolerate the human centromere better than mice and, unlike mice, are rarely mosaic. Research using human induced pluripotent stem cells (iPSCs) is moving forward. Investigators can now use patient-derived iPSCs to study conditions common in people with DS, such as congenital heart defects, intellectual disability, and AD. More researchers are now using three-dimensional cell cultures that allow cells to self-organize into organoids. This method supports greater numbers of cell types and cell interactions than two-dimensional cell cultures. Another presentation described research generating neuronal cell lines containing the presenilin mutation from patients with familial AD to use in three-dimensional cultures. This presentation also described studies of the role of extracellular vesicles in AD pathogenesis.

## **Day 2 Session on Cohort Development: INCLUDE Data Coordinating Center and Existing and Future Cohorts**

NIH has funded multiple projects in support of development of DS cohort studies. One such effort involves creation of a data coordinating center (DCC) and a data portal to standardize, harmonize, and aggregate DS data into a virtual biorepository, with a goal of providing data access and analysis tools for transformative DS research. The findings of a survey of 57 existing cohorts and databases related to DS research will serve as a starting point for the DCC. Another presentation described a variety of options for linking data, including Global

Unique Identifiers (GUIDs), PCORnet, Datavant, and a referral code model that is being used in the DS-DETERMINED study. The Biospecimen Working Group has recommended that blood, brain tissue, cerebrospinal fluid, saliva, cord blood, surgical specimens, urine, and stool be collected for DS cohort studies. During the discussion, attendees suggested collecting additional biospecimens, including liver tissue, heart tissue (myocardium), vascular specimens, autopsy specimens, amniotic fluid from prenatal diagnoses, and placental tissue. The importance of linking biospecimens with clinical data and consents was emphasized. Attendees suggested leveraging DS-Connect®: The Down Syndrome Registry to consent participants to broad sharing from all past studies and to facilitate online consent for people with DS so they can readily provide a research blood sample during a routine visit to the doctor.

## Day 2 Breakout Sessions and Reports

Breakout Groups 5 (Ensuring Robust iPSC and Organoid Systems as Preclinical Models) and 6 (Ensuring Robust Animal Model Systems as Preclinical Models) discussed how to choose the best model system and ensure rigor and responsibility and determine what clinical and epidemiological data and biospecimens are needed for basic science studies. Both groups concluded that the model depends on the scientific question being asked and the analyses to be done, and they offered strategies for enhancing rigor and reproducibility. Group 5 said desirable data and biospecimens included clinical data on early brain development, cancer, iPSC lines from diverse populations (accompanied by related clinical data), plasma biomarkers, and a registry of all available DS cells. Group 6 suggested clinical, cognitive, and disease phenotypes to aid mouse-to-human translation, cross-comparative data on mouse phenotypes, clinical data on circadian rhythms and sleep, drug testing data, respiratory and infectious disease natural history data, and samples from brain biobanks.

Breakout Groups 7 (Clinical Phenotyping and Minimal Common Data Elements) and 8 (Biospecimens and Related Omics Datasets) discussed what biospecimens and clinical and phenotyping data should be collected and what clinical scenarios and fundamental scientific questions should be addressed by a large cohort study. The two groups suggested collecting basic medical history data across the lifespan, behavioral and cognitive metrics, and environmental data. Both groups emphasized that biospecimens must be linked to phenotypic data. They suggested collecting the biospecimens recommended during the cohort development concurrent session, along with a few of their own additions. Fundamental clinical and scientific matters included identifying the risk and protective factors associated with DS co-morbidities, conducting network gene analyses to determine which genes cause which phenotypes, and identifying the unique transcriptomic signatures in specific tissues of relevance to DS, such as heart and lung.

## Panel Discussion

Six invited DS investigators were asked to discuss what basic scientists want clinical investigators to know and what clinical investigators want basic scientists to know. The panelists all agreed that communication with DS research participants must be done in a way that does not make them feel devalued. Researchers should try to minimize the time commitment for participants and their families, who give so generously of their time, and should consider ways to incentivize participants' research experience. The basic science side must define the problems to be addressed, and investigators must ensure that clinical data are detailed and broken out into collective phenotypes in clinical trials. Investigators also need to think about what biomaterials will be needed in the future. The panelists suggested that future collaborative efforts should build on the dialogue among basic science and clinical investigators, people with DS and their families, and advocates that was such a valuable part of this workshop.

## Next Steps and Closing

The feedback from this meeting will inform the NIH DS research plan, which is to be published in 2021. Dr. Parisi thanked everyone who had been part of the working groups that are so critical to this field and everyone who participated in this meeting and provided such important feedback and information.