

Subcommittee on Health on Wednesday, February 14, 2024, to testify at the hearing entitled  
“Legislative Proposals to Support Patients and Caregivers”

Attachment — Additional Questions for the Record

**The Honorable Robert Latta**

**People with Down syndrome are the largest population with a genetic predisposition to Alzheimer’s disease yet for decades were not included in this vital research. Can you share in more detail how the INCLUDE initiative and the legislation before the committee today will advance science and lead to the discovery of Alzheimer’s disease treatments for people with Down syndrome and typical Americans?**

Thanks to the INCLUDE Project, there are now large studies of adults with Down syndrome at risk of Alzheimer’s disease, including both observational cohort studies and clinical trials. For example, the INCLUDE Project supports a large cohort study (more than 400 participants) to discover early biomarkers of Alzheimer’s disease in Down syndrome, known as the Alzheimer Biomarkers Consortium Down syndrome (ABC-DS). In another example, the INCLUDE Project is supporting a clinical trial network to test novel therapies for Alzheimer’s disease in Down syndrome known as the Trial Ready Cohort Down Syndrome (TRC-DS). Furthermore, the INCLUDE Project is also funding a clinical trial for a novel immunomodulatory medicine for Alzheimer’s disease known as Leukine/Sargramostin. Additionally, the INCLUDE Project is funding many basic science studies aimed at elucidating the mechanisms by which the extra copy of chromosome 21 causes this increased risk of Alzheimer’s in this population. Moving forth, this legislation will ensure that these efforts are expanded and enlarged, leading to the eventual approval of novel diagnostics and therapeutics for Alzheimer’s disease in Down syndrome and potentially in typical people without Down syndrome.

**Prior to INCLUDE, there were few if any Down syndrome clinical trials and most clinical trials excluded people with Down syndrome from participating. In the six years since INCLUDE was established, there are now at least 12 clinical trials that include repurposed drugs to treat autoimmune diseases, Alzheimer’s, cognition deficit, and Regression Disorder. Can you explain the role that INCLUDE has played in this turnaround and how the bill will continue this important work?**

The INCLUDE Project has been the key driver of this turnaround. In fact, the first batch of INCLUDE-funded clinical trials are now completing activities and their results will be available soon. These trials include interventions to address the high burden of autoimmune conditions, obstructive sleep apnea, attention deficit and hyperactivity disorders, and Alzheimer’s disease in this population. This legislation will ensure that these Phase I and Phase II trials continue into Phase III trials that would lead to eventual FDA approval for new therapies. Naturally, this legislation will also ensure the continued deployment of new clinical trials addressing the co-occurring conditions of Down syndrome.

**It is my understanding that people with Down syndrome may not respond to certain FDA approved treatments that are prescribed for typical people and in some instances FDA approved treatments for certain chronic diseases can even be harmful for people with Down syndrome. Can you share more detail on the types of drugs and conditions that GLOBAL is studying and what your scientists are learning as a result of support provided as part of INCLUDE?**

There is no comprehensive assessment of how people with Down syndrome may respond to various medicines with diverse mechanisms of action. Given that most FDA-approved medicines were tested only in the general population, it is critical to understand how people with Down syndrome may respond, either better or worse, to these interventions. For example, clinical trials at the Crnic Institute are testing a class of FDA-approved immune therapies known as JAK inhibitors with the goal of decreasing the burden of autoimmune conditions in this population. Another INCLUDE-trial is testing FDA-approved medicines for ADHD in Down syndrome. These studies will help address if these medicines are safe and effective and whether their dosing needs to be modified in people with Down syndrome.

**People with Down syndrome are highly protected from developing solid tumors – like breast cancer or prostate cancer – yet are highly predisposed to certain blood cancers like acute megakaryoblastic leukemia (AMKL) and acute lymphoid leukemia (ALL). Can you explain the connection and how INCLUDE supported research is unlocking these secrets and pointing us in the direction of new treatments?**

It is now well demonstrated that people with Down syndrome have a different malignancy spectrum, with increased risk of leukemias early in life and decreased risks of solid malignancies throughout the lifespan. However, the mechanisms driving these differences are unknown. Some scientists hypothesize that this could be driven by differences in their immune system, leading to more blood malignancies but increased 'tumor surveillance' of solid tumors. Others hypothesize that there may be leukemia-driving genes and tumor-suppressive genes on chromosome 21, which is triplicated in those with Down syndrome. This different malignancy spectrum could also be due to metabolic differences. Clearly, additional research in this area could lead to discoveries that would also benefit the general population.

### **The Honorable Gus Bilirakis**

**Thank you for your support of the Congenital Heart Futures Reauthorization Act of 2024. Can you provide any insight or recommendations for how you believe we can improve the existing Congenital Heart Defect program at the CDC and explain why we need to better educate the public about the challenges that persist for congenital heart patients, especially patients with Down Syndrome?**

INCLUDE-funded research has demonstrated an important role for *in utero* immune dysregulation as a driver of congenital heart defects in mouse models of Down syndrome, pointing to a set of genes known as interferon receptors as the culprit. These and other studies illustrate how the study of the co-occurring conditions of Down syndrome can advance other research fields. For example, the Congenital Heart Defect program at the CDC may consider a comprehensive assessment of maternal immune activation (e.g. infections during pregnancy) that could contribute to increased risk of congenital heart defects in the general population.