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Submitted by email at DownSyndrome@mail.nih.gov

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Re: NOT-HD-21-014 - Comment on the Draft NIH INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE (INCLUDE) Down Syndrome Research Plan

Dear Dr. Parisi:

The National Down Syndrome Society (NDSS) and LuMind IDSC Foundation (LuMind IDSC) appreciate the opportunity to provide comments on the draft NIH INCLUDE Down Syndrome Research Plan. We also want to express our appreciation to you, Dr. Diana Bianci, Dr. Francis Collins, the team at NICHD, and the full leadership of the National Institutes of Health (NIH) in helping to bring the Down syndrome community together around the focused and achievable research objectives outlined in the draft plan.

Overall, we support the draft plan, which is broad in scope, grounded in current scientific thinking, and informed by a wide spectrum of scientific and health care practitioners. More importantly, we believe the draft plan, if fully implemented, will advance the treatments and interventions that will dramatically improve the health and well-being of individuals with Down syndrome by the end of the decade.

As you know, in response to NIH's April 2020 Request for Information (NOT-HD-20-013), our organizations jointly submitted comprehensive recommendations developed by more than 50 researchers, scientists, clinicians, medical providers, caregivers, advocates (including self-advocates), and local, national, and international representatives from Down syndrome organizations.

We commend NIH for incorporating most of those recommendations in various forms of specificity into the draft plan. Therefore, our comments hereafter focus primarily on issues of implementation and clarification.

Revise the Research Plan Title – We recommend that the title of the research plan articulate a clear vision of success by the end of the decade, recognizing the limitation of the current scientific knowledge base. Therefore, instead of "NIH INCLUDE Down Syndrome Research Plan," we recommend as the title "Down Syndrome 2030: Achieving Research Breakthroughs Across the Lifespan." This title better reflects the need for substantial progress in meeting the critical health and quality-of-life needs for individuals with Down syndrome, and what is achievable by the end of the decade.

Establish Timelines – In each of the broad categories of research plan goals and objectives, we encourage the inclusion of timelines. We recognize that many of the timelines will be aspirational, but we encourage their inclusion as a way to focus the attention of the research community around what is achievable and where funding will be focused.

Make the INCLUDE Project Permanent – Organizing a trans-NIH research initiative under the direction of the NIH Director has elevated the visibility and importance of Down syndrome research and the contributions being made by scientists and clinicians in addressing the critical health and quality-of-life needs for individuals with Down syndrome. The INCLUDE project has provided increased access to each of the Institutes whose tissue- and disease-based agendas are germane to Down syndrome. We agree that it has helped to recruit new talent to the base of Down syndrome researchers, and significantly facilitated outreach to scientists whose work, while relevant to Down syndrome, is not currently directed at Down syndrome. To ensure that this momentum is sustained, and to achieve the full promise of the robust program outlined in the draft research plan, it is critical that the INCLUDE Project be made permanent with a stable and dedicated funding stream.

Expand Access and Participation – We strongly support the draft plan's stated need to include people with Down syndrome of different ages, socioeconomic levels, and racial and ethnic diversity in research. This challenge increases in complexity as people with Down syndrome age. One option for advancing inclusion and increasing overall participation in both basic and clinical research is to support the establishment of a DS Clinical Care Network consisting of specialty centers in large population areas focused on improving care for patients with Down syndrome. In addition to providing high quality care and educating community providers, such centers would facilitate NIH funded research by collecting clinical and demographic data and recruiting patients for studies and clinical trials. Unfortunately, there are few specialty clinics in the U.S. that serve adults with Down syndrome. According to a recent survey, there are 25 clinics that care for adults with Down syndrome, meeting the needs of just five (5) percent of the population[1]. Expanding capacity through a DS Clinical Care Network would dramatically increase access and participation in the research prioritized by the draft plan.

Clarification of Specific Goals and Objectives – On page 13, under the section "Expand Research to Understand the Impact of Common Co-Occurring Medical Conditions in DS on Cognition and Overall Health Outcomes," please consider including the following:

- Study the mechanisms by which trisomy 21 increases susceptibility to and/or severity of autoimmune diseases in people with DS, such as which SNPs, genes and/or signaling

[1] https://onlinelibrary.wiley.com/doi/abs/10.1002/ajmg.a.62169

pathways may be implicated, and how these differ from typical individuals with autoimmunity.

- Evaluate the need for additional tools to identify pathologic antigen-specific cells driving autoimmunity in people with DS.

- Thoroughly investigate the possible autoimmune etiology of co-occurring conditions in people with DS, for example antibody-negative hypothyroidism.

On page 15, under the section "Study obstructive sleep apnea (OSA) and other sleep-related disorders," the efficacy of available diagnostic tools is mentioned as a focus of study. Please consider expanding the diagnostic topic with the following:

- Study the feasibility and validation of at-home diagnostic tools including actigraphy, home sleep apnea testing, and wearable technologies.

Under "Enhancing Quality of Life" beginning on page 17, please consider the following:

- In the fourth bullet on page 18, the beginning of the first sentence should be restated to say "Evaluate the benefits of alternative and augmentative communication …" as this better describes the interventions that foster communicability in people with Down syndrome.

- Generally, the discussion of "Enhancing Quality of Life" could benefit from a more fulsome mention of education and academics (including literacy) and the connection to how these areas support success in post-secondary education and job opportunities. Similarly, additional discussion of the need to support the transition from high school to adulthood and for functioning/job skills training would highlight an important opportunity for enhancing quality of life.

Thank you, again, for leading the Down syndrome research community around a comprehensive and unified plan and strategy to address the many scientific gaps that hinder efforts to meet the critical health and quality-of-life needs for individuals with Down syndrome and their families. Our organizations recognize that, for these recommendations to achieve their desired result, a coordinated approach with other funders of research, including other U.S. government agencies and non-government organizations, is needed. Therefore, we look forward to working with you to advance that approach.

Sincerely,

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