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Comments Regarding

Draft National Plan To Address Alzheimer's Disease

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Thank you for the development of the Draft National Plan to Address Alzheimer's Disease, and for the opportunity to submit comments.

The Down Syndrome Research and Treatment Foundation is a national/international 501(c)(3) nonprofit organization with the mission to stimulate and support biomedical research that will accelerate development of treatments to significantly improve cognition, including memory, learning and speech, for children and adults with Down syndrome. The major objectives include creating new opportunities for all Individuals with Down Syndrome to: 1) Lead more independent lives; 2) Participate more successfully in schools & employment; and 3) Prevent additional early cognitive decline with aging & Alzheimer's disease. Since its founding in 2004, DSRTF, through its novel research strategy and grants program, has identified and substantively supported much of the research that has led to the recent rapid and unprecedented advances in Down syndrome cognition research and the first clinical trial with a novel drug candidate to focus on as a primary indication and specifically address overcoming cognitive and behavioral impairments in individuals with Down syndrome by a major international pharmaceutical company, Roche.

We acknowledge and appreciate the explicit recognition, inclusion and designation of attention to intellectual disabilities populations as unequally burdened by Alzheimer's disease within Strategy 2.H: Improve care for populations disproportionally affected by Alzheimer's disease and for populations facing care challenges. However, this is far too limited within the overall plan; it is more than just initiatives addressing only care. As discussed further below, there is a very strong rationale to explicitly include Down syndrome in each of the strategies, and designated strategic sub-actions, comprising the National Alzheimer's Plan and resulting initiatives, and Strategy 1 involving fundamental, translational and clinical research in particular.

As research has documented, virtually all individuals with Down syndrome, now numbering more than 400,000 individuals in the US, develop the characteristic neuropathology associated with Alzheimer's disease by age 40. Research has also shown that, very conservatively, at least

25% increasing to 75% or more of the individuals with Down syndrome between the ages of 40-60 develop the signs and symptoms of Alzheimer's-type dementia and the percentage increases with age. These facts underscore the very significant and important relevance of this population as a key and explicit element to be included not only in the National Alzheimer's Plan but also in the development and implementation of all aspects of the Plan, including research (fundamental, translational, and clinical) to effectively prevent and treat Alzheimer's disease, enhancing care quality and delivery, and expanding supports for people with Alzheimer's disease and their families. Given these facts, explicit and integral inclusion and consideration of Down syndrome in the Plan and associated initiatives can not only significantly address the significant number of individuals with Down syndrome but also the larger non-Down syndrome population developing or with Alzheimer's disease. This requires significant increases in awareness and rational considerations among researchers and clinicians, which can be partly addressed through explicitly including Down syndrome more prominently in the Plan as well as in resulting initiatives and increased proportional funding.

Given the significant size of the Down syndrome population (>400,000 in the US, and up to 10-times that number worldwide) and the virtual certainty that the individuals will develop the characteristic neuropathology of Alzheimer's disease and ultimately the associated dementia further compromising their cognition and life, inclusion of Down syndrome, particularly in the research initiatives (fundamental, translational, and clinical) would significantly contribute important novelty, unavailable otherwise, to as well as enhance and accelerate essentially all aspects of the major objectives specified under Goal 1: Prevent and Effectively Treat Alzheimer's Disease by 2025 as well as Goal 2. NIH grants and funding for <u>all</u> of Down syndrome research have remained disproportionately very low, e.g. $20M in FY 2011. This includes a much smaller and too limited subset of research grants investigating the aspects of Alzheimer's disease associated with Down syndrome. As only one contrasting example, explicit and significant attention and funding by NIH and its Alzheimer's disease research initiatives, both basic and translational, have been targeted to so-called dominantly inherited Alzheimer's disease, both basic and translational (see e.g., the DIAN initiative) that is much more rare and with a much smaller population. In both Down syndrome and dominantly inherited Alzheimer's disease myriad research has confirmed the significant involvement of the same gene, APP, and its products (The APP gene is located on human chromosome 21, the chromosome trisomic in Down syndrome, as are a number of additional genes demonstrated to be involved in mechanisms associated with Alzheimer's disease.). Through more detailed and sufficient investigations in the Down syndrome population, researchers can obtain invaluable insight into how and why Alzheimer's disease develops, and can compare and extend their findings to the much more common late-onset sporadic Alzheimer's disease as well as enhance and accelerate development of new therapeutics. The relevant trajectory to Alzheimer's disease and size of the Down syndrome population provides a strong rationale for greater recognition and explicit inclusion in the National Alzheimer's Disease Plan and resulting Alzheimer's disease fundamental, translational and clinical research initiatives.

Although by no means an attempt to thoroughly include detailed or exhaustive rationale and recommendations in these comments here, in addition to the suggestions and requests above

with respect to more prominent and explicit integral recognition and inclusion of Down syndrome in the ultimate version of the National Alzheimer's plan, I submit the following recommendations for further consideration:

- Explicitly recognize and include discussion and components specifically involving Down syndrome in Goal 1 as well as each of the proposed "Actions" under Strategy 1A, including Actions 1.A.1-5.
- Explicitly recognize and include discussion and components specifically involving Down syndrome in Strategy 1.B. including Actions 1.B.1-6. This would include not only research in animal models of Down syndrome, but with respect to human clinical studies explicit designation and inclusion of relevant and appropriate cohorts of individuals with Down syndrome, together with and/or in parallel/addition to those clinical studies initiatives involving non-Down syndrome cohorts. The results would be expected to be mutually informative and beneficial.
- Explicitly recognize and include discussion and components specifically involving Down syndrome in Strategy 1.C. including Actions 1.C.1-2. Again, given that essentially every individual with Down syndrome develops the characteristic neuropathology associated with Alzheimer's disease by age 40 with a significant proportion also developing the signs and symptoms of Alzheimer's-type dementia and further increases with age earlier, inclusion of relevant and appropriate cohorts of individuals with Down syndrome, together with and/or in parallel/addition to these research initiatives involving non-Down syndrome cohorts would uniquely provide important relevant and additional information, insights, direction and acceleration of success.
- As is true for Alzheimer's disease research and development, relevant Down syndrome research is ongoing, and increasing, internationally. It will be important to coordinate with and expand relevant Down syndrome research internationally and collaboratively. Therefore, explicitly recognize and include discussion and components specifically involving Down syndrome in Strategy 1.D. including Actions 1.D.1-2.
- Explicitly recognize and include discussion and components specifically involving Down syndrome in Strategy 1.E. including Actions 1.E.1-3. With respect to Action 1.E.1., again, given that essentially every individual with Down syndrome develops the characteristic neuropathology associated with Alzheimer's disease by age 40 with a significant proportion also developing the signs and symptoms of Alzheimer's-type dementia and further increases with age earlier, inclusion of relevant and appropriate cohorts of individuals with Down syndrome, together with and/or in parallel/addition to these research initiatives involving non-Down syndrome cohorts would uniquely provide important relevant and additional information, insights, direction and acceleration of success. With respect to Action 1.E.2., inclusion of private-public collaborations and partnerships between Federal entities such as NIH and non-governmental nonprofit organizations such as DSRTF with its focus on Down syndrome cognition research will enhance productivity, accelerate significant progress and success as well as minimize duplications of efforts and resources. With respect to Action 1.E.3., the critical

importance of the increasing development and very significant impact of Alzheimer's disease on individual with Down syndrome and their families and care givers underscores the importance of involvement and communication with this community and associated stakeholders.

- As indicated above, given the particular and significant relevance and importance of and impact of Alzheimer's disease on the relatively large population of individuals with Down syndrome, their families and caregivers as well as the healthcare system, it is not sufficient to generally designate "intellectual disabilities" in only Strategy 2.H. "Down syndrome" should be explicitly included in proposed Strategies 2.A.-H., 3.A.-E., 4.A.-B. and each of the Actions included under those strategies. Therefore, explicitly recognize and include discussion and components specifically involving Down syndrome in Strategies 2.A.-H., 3.A.-E., 4.A.-B. and each of the Actions included under those strategies.
- Finally, based on the comments, rationale and recommendations outlined above, we would encourage and recommend that a representative from the Down syndrome community be added to the National Alzheimer's Project Act (NAPA) Advisory Council, as the important deliberations, priorities and implementation will have mutual benefits to science/research, clinical care, and long term care not just additionally for individuals with Down syndrome and associated Alzheimer's disease but also for the broader population and research efforts involving Alzheimer's disease.

I would be very pleased to further discuss, as may be helpful and informative, any aspects of the above concerning the importance of explicit inclusion and considerations of Down syndrome relating to Alzheimer's disease in further detail with those involved in developing the National Plan, including members of the Advisory Committee. I have registered for and plan to attend the upcoming May 14-15 NAPA/NIH Alzheimer's Disease Research Summit in Bethesda, and look forward to the opportunity for further discussion of the importance and relevance of Down syndrome for the Plan and its successful implementation as outlined above.