STATEMENT REGARDING THE AA REVISED CLINICAL CRITERIA

Submitted: November 16, 2023

Joint comments on behalf of the LuMind IDSC Foundation (www.lumindidsc.org) and the National Task Group on Intellectual Disabilities and Dementia Practices (www.the-ntg.org) regarding the Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Association Workgroup.

Background: *The National Institute on Aging and the Alzheimer's Association (NIA-AA) draft diagnostic guidelines on diagnosing Alzheimer's disease were issued in July at the 2023 AAIC Conference in Amsterdam, NL, with a request for comments. A subsequent, revised, updated version was issued solely by the Alzheimer's Association at the Clinical Trials on Alzheimer's Disease (CTAD) conference on Oct. 25, 2023, with a call for further comments. In response, the LuMind IDSC Foundation and the NTG jointly submitted the following comments.*

The LuMind IDSC Foundation and the National Task Group on Intellectual Disabilities and Dementia Practices vigorously support the AA revised clinical criteria for Alzheimer's disease. Key recommendations pertinent to Down syndrome-associated Alzheimer's disease (DS-AD) and our comments for these recommendations are:

1. **Down syndrome should be considered Stage 0 Alzheimer's disease.** We concur that this separate stage 0 should recognize Down syndrome and other genetically determined Alzheimer's disease. This recommendation is appropriate and justified by the pathophysiology of DS-AD, which is comparable to other forms of AD such as LOAD, and the fact that DS-AD is a genetic form of AD that is highly penetrant (up to 95%, McCarron et al. 2017) and with average age of symptom onset in the mid-50s (Iulita et al. 2022) in the DS population.

2. **AD diagnosis using plasma biomarkers should be an objective as part of the biological diagnostic criteria.** As the draft revision states: *The most significant advance in AD diagnostics in recent years has been the development of plasma biomarkers with excellent diagnostic performance. This now makes biological diagnosis of AD (which previously required PET or CSF assays) accessible and is projected to revolutionize research and clinical care.* We endorse the recommendation to move toward biological criteria for diagnostic staging of AD through plasma biomarkers, but in the case of DS-AD, the plasma biomarkers being rapidly developed for the general population have not been validated for the DS population, which requires separate plasma biomarker cut-points to be established or LOAD cut-points to be confirmed to be the same in DS-AD. For example, cut-points that correlate A+ by Aβ PET with plasma Aβ42/40 or p-tau217 have not been determined yet. Therefore, the plasma biomarkers are not accessible yet for early AD diagnosis in the DS population. We recommend noting any variations in cut-points specific to Down syndrome as they are determined.

3. **Categorization of fluid analyte and imaging biomarkers may slightly differ in DS-AD.** NFL is categorized in Table 1 as a "Biomarker of non-specific processes involved in AD pathophysiology". In DS-AD where the AD population is younger and there are less co-occurring neurodegenerative diseases, NFL is more likely to be caused by AD than it is in LOAD. We recommend adding a comment to that effect after the Table 1.

4. **Progression in the biological stages might be accelerated in DS-AD.** Based on recent data from Wisch et al. under submission, tau pathology acceleration in DS-AD is significantly faster in DS-AD than in ADAD. We recommend adding below Table 6 a comment to that effect or by extending the sentence with the words in italic "… will often be due to co-morbid pathology *or from having Down syndrome*."

5. **Diversity should include considerations for the DS population and for other populations with neuroatypical conditions.** We recommend adding to Item (10), page 26, line 792 ff., "Diversity and need for more representative cohorts," language to include adults with Down syndrome and with various lifelong neuroatypical conditions, including intellectual disabilities, in more observational studies, clinical trials and post-marketing studies.

The Down syndrome population served as a key resource for the research and discovery of the pathobiological basis for AD, yet this population is being left behind for diagnostic and therapeutic access to disease modifying therapies. We strongly recommend the inclusion of people with Down syndrome in on-going and future observational studies that determine the biological criteria for the presence of Alzheimer's disease or other forms of dementia.

We thank you for including the Down syndrome population in this Revised Criteria for Diagnosis and Staging of Alzheimer's Disease as it will help address important inequities that this population is still facing.

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Iulita MF, Garzon Chavez D, Klitgaard Christensen M et al. Association of Alzheimer disease with life expectancy in people with Down syndrome. *JAMA Netw Open.* 2022;5(5):e2212910. doi:10.1001/jamanetworkopen.2022.12910

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