



August 30, 2023

National Institute on Aging
31 Center Drive
Bethesda, MD 20892

Alzheimer's Association
225 N. Michigan Ave, Floor 17
Chicago, IL 60601

RE: NDSS Comment on the Draft NIA-AA Revised Clinical Guidelines for Alzheimer's

Dear National Institute on Aging and Alzheimer's Association:

The National Down Syndrome Society (NDSS) empowers individuals with Down syndrome and their families by driving policy change, providing resources, engaging with local communities, and shifting public perceptions. We write today in response to the National Institute on Aging (NIA) and Alzheimer's Association draft Revised Clinical Guidelines for Alzheimer's. Given that there has been significant progress in the scientific and clinical understanding and diagnosis of Alzheimer's disease since 2018, NDSS applauds the NIA and the Alzheimer's Association for convening a workgroup to update and enhance the clinical guidelines for Alzheimer's disease. **Furthermore, NDSS strongly supports the explicit inclusion of the Down syndrome community in the guidelines (Section 5.2, Stage 0 and genetics) and urges the NIA and the Alzheimer's Association to ensure that these new diagnostic criteria are included in the final guidelines.**

Individuals with Down syndrome are uniquely situated in the Alzheimer's landscape because they have an extra copy of chromosome 21. The 21st chromosome carries the amyloid precursor protein (APP) gene, which is strongly associated with the formation of amyloid peptides and plaques, a hallmark of Alzheimer's disease. As a result, individuals with Down syndrome have an elevated lifetime risk – higher than 90% – for developing Alzheimer's disease (the combination is referred to as DSAD), with the onset of symptoms coming earlier and progressing faster than in the general population.¹ In fact, Alzheimer's disease is the number one cause of death for individuals with Down syndrome.²

Unfortunately, Alzheimer's disease is commonly misdiagnosed in patients with Down syndrome. Often, this is because Alzheimer's Disease and Down syndrome share some observable traits, leading many physicians to attribute behaviors to Down syndrome without testing to see if these traits are because of the onset of Alzheimer's Disease - an issue called diagnostic overshadowing. Given this prognosis, it is critical that researchers, clinicians, and community members have an increased understanding of the diagnosis of Alzheimer's disease in the general population and DSAD that is rooted in clinical evidence and pathology, not just observable traits.

¹ McCarron, M., McCallion, P., Reilly, E., Dunne, P., Carroll, R., & Mulryan, N. (2017). A prospective 20-year longitudinal follow-up of dementia in persons with Down syndrome. *Journal of intellectual disability research* : JIDR, 61(9), 843–852. <https://doi.org/10.1111/jir.12390>

² Hithersay, R., Startin, C. M., Hamburg, S., Mok, K. Y., Hardy, J., Fisher, E., Tybulewicz, V., Nizetic, D., & Strydom, A. (2019). Association of Dementia With Mortality Among Adults With Down Syndrome Older Than 35 Years. *JAMA neurology*, 76(2), 152–160. <https://doi.org/10.1001/jamaneurol.2018.3616>



Section 5.2, *Stage 0 and genetics*, proposes the addition of stage 0, which explicitly acknowledges the unique genetic predisposition that individuals with autosomal dominance and Down syndrome (Trisomy 21) have for developing symptoms and the clinical onset of Alzheimer’s disease. Furthermore, the creation of stage 0 stipulates that an individual would only move to stage 1 “when core biomarker(s) become positive.” For individuals with Down syndrome who present across a broad spectrum of cognitive and executive function, this focus on objective diagnostic biomarkers helps ensure diagnostic overshadowing does not negatively impact an individual’s diagnosis or subsequent treatment for Alzheimer’s disease but instead, these diagnoses and treatment plans are based in clinical pathology.

As noted in the guidelines, this proposal is consistent with recent proposals for diseases such as Huntington’s and Parkinson’s disease and is warranted given the latest advancements in the understanding and diagnosis of Alzheimer’s disease. As researchers’ understanding of the genetic and pathologic indicators of the disease improves, so too should the criteria clinicians use to diagnose the disease so that more accurate diagnoses can be made and ultimately treatment plans and outcomes can be more informed and effective.

The inclusion of Section 5.2 could positively impact the Down syndrome community in a number of ways including, but not limited to – **increasing education, diagnostic efficacy, and access** for those with DSAD, **elevating the status** of the Down syndrome community within the field, and **changing the narrative** around quality of life and expected outcomes of DSAD.

Increasing Education, Diagnostic Efficacy, and Access

Despite being adversely affected by Alzheimer’s at a rate that is markedly higher than that of the general population, or any other underserved population, the Down syndrome community continues to face barriers to accessing high quality diagnostic, treatment, and care options. This can be attributed, at least in part, to the lack of education and awareness of the connection between Down syndrome and Alzheimer’s disease and how DSAD compares to Alzheimer’s disease in the general population.

Research supports that there is little to no genetic difference between Alzheimer’s disease in the general population and DSAD, and therefore, drugs and treatments that are found to be effective for the general population will very likely have the same efficacy for those with DSAD.^{3 4} These treatments may, however, pose additional or increased rates of symptoms or complications from what is typically observed in the general population. Inclusion in clinical trials and the development of safety data that is inclusive of, and specific to, the Down syndrome community is necessary to ensure

³ Fortea J, Zaman SH, Hartley S, Rafii MS, Head E, Carmona-Iragui M. Alzheimer’s disease associated with Down syndrome: a genetic form of dementia. *Lancet Neurol.* 2021;20(11):930-942. doi:10.1016/S1474-4422(21)00245-3

⁴ Boerwinkle AH, Gordon BA, Wisch J, et al. Comparison of amyloid burden in individuals with Down syndrome versus autosomal dominant Alzheimer’s disease: a cross-sectional study. *Lancet Neurol.* 2023;22(1):55-65. doi:10.1016/S1474-4422(22)00408-2



individuals with DSAD can *safely* benefit from the drugs and treatments the general population is prescribed.

The cornerstone to establishing these trials and the prescription of any promising drug or treatment is a clinician's ability to diagnose Alzheimer's disease confidently and objectively in a patient with Down syndrome. Thus, the inclusion of diagnostic criteria specific to DSAD in the revised clinical guidelines is paramount to ensuring that clinicians are educated about DSAD, have the tools necessary to diagnose DSAD based on the clinical pathology, and ultimately, that individuals with DSAD will have equitable access to the interventions they so desperately need.

Lastly, these clinical guidelines will also be invaluable to the INCLUDE (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromeE) Project, a trans-NIH research initiative on critical health and quality-of-life needs for individuals with Down syndrome that promotes the inclusion of people with Down syndrome into clinical trials, and the NIA's Alzheimer's Clinical Trials Consortium – Down syndrome (ACTC-DS), which exemplifies the innovative efforts needed to ensure that people with Down syndrome benefit from recent advances in Alzheimer's disease diagnostics and therapeutics. The incorporation of diagnostic criteria specific to the Down syndrome community will support these two entities in their work to advance clinical trials designed for people with Down syndrome.

Elevating the Status

Beyond the immediate impact on clinicians, the inclusion of this proposed diagnostic criteria also has the potential to have a wide-reaching impact on regulatory agencies, drug developers, researchers, and families. Criteria specific to the diagnosis of DSAD will help bring familiarity of the co-occurrence to drug developers that could lead to further developments in the treatment and cure of Alzheimer's disease for patients with Down syndrome. Additionally, bringing a focus to the unique presentation and diagnosis of DSAD could urge researchers and clinicians to consider new and innovative treatments that could potentially impact thousands of people within the Down syndrome community.

Lastly, as the understanding of DSAD continues to develop, it is our hope that regulatory agencies will ensure that individuals with Down syndrome are able to fully access all drugs and treatments available and prescribed by their physician following a diagnosis based in clinical pathology and individualized assessment. Including the Down syndrome community in the revised clinical guidelines is the first step toward elevating the status of the Down syndrome community throughout the field and ensuring that all decision makers have the information they need to make informed decisions about the development, prescription, and coverage of drugs and treatments.



Changing the Narrative

For far too long, the same somber sentiment has been echoed within the Down syndrome community – “it is not *if*, but *when*.” With lifetime risk rates for developing Alzheimer’s disease climbing over 90%, parents, caregivers, and individuals with Down syndrome too often live in fear of an intangible disease that they have been told they or their loved one will almost certainly develop. As a community-facing advocacy organization, NDSS feels strongly that it is the role of organizations like ours to partner with agencies, researchers, drug developers, and clinicians to change this narrative. A disease that once seemed untreatable is now becoming treatable. A community that has for so long lived in fear can now begin to live in hope. Once again, we urge the NIA and the Alzheimer’s Association to ensure that Section 5.2 of the proposed guidelines is included in the final revised clinical guidelines and to work with organizations like ours to continue changing the narrative for the Down syndrome community.

NDSS strives to ensure all individuals with Down syndrome are assured their human rights and valued by a more inclusive society. We applaud the Alzheimer’s Association, the NIA, and the working group for their work on this critical issue and look forward to continuing to work together toward a more equitable and inclusive diagnostic landscape for the Down syndrome community.

Sincerely,

A handwritten signature in black ink that reads "Kandi Pickard". The signature is fluid and cursive, with a large loop at the end of the last name.

Kandi Pickard
President and CEO
National Down Syndrome Society