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## Down Syndrome in a New Era for Alzheimer Disease

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US Food and Drug Administration–approved disease-modifying treatments for Alzheimer disease are now available by prescription. This recent approval is based on evidence from large randomized, placebo-controlled trials of amyloid-lowering immunotherapies, which have demonstrated that reducing amyloid plaques results in improved outcomes in patients with early-stage Alzheimer disease.<sup>1,2</sup> However, adults with Down syndrome, who have a genetically defined form of Alzheimer disease, have not been included in any of these trials. In fact, only a small number of clinical trials for Alzheimer disease have been conducted that include people with Down syndrome.<sup>3</sup>

There are approximately 6 million individuals with Down syndrome across the globe, and they comprise the largest population with genetically determined Alzheimer disease in the world. Virtually all individuals with Down syndrome develop amyloid plaques by the age of 40 years, and more than 95% will develop Alzheimer disease dementia by their seventh decade, with average age of dementia onset being 54 years.<sup>3</sup> Due to advances in health care, people with Down syndrome are living longer, healthier, and more independent lives, with the fastest growing segment of this unique population being older than 50 years.<sup>3</sup> With this change in life expectancy, Alzheimer disease is now the leading cause of mortality in adults with Down syndrome older than 35, being the proximate cause of death in 70% of cases.<sup>4</sup> As a result of this mortality risk, individuals with Down syndrome have a substantial 20-year gap in life expectancy compared with the general population. Addressing this disparity will require developing and evaluating effective Alzheimer disease–modifying therapies.

Despite this ultra-high risk for Alzheimer disease and its effect of a shortened life expectancy, persons with Down syndrome who are experiencing Alzheimer disease–related cognitive decline have limited access to expert clinical evaluation for dementia, let alone these newly approved therapeutics. At the same time, because of the genetic basis for lifelong amyloid accumulation, there are also significant concerns related to cerebral amyloid angiopathy and the risk of adverse events related to amyloid-related imaging abnormalities (ARIA).<sup>5</sup> This fact requires careful assessment of safety and tolerability in individuals with Down syndrome to be done before these drugs can be widely prescribed

in this vulnerable population. Current appropriate use recommendations that have been published for lecanemab specifically advise against treating persons with Down syndrome until safety studies are completed.<sup>6</sup>

These challenges have brought forth a quandary. The first consideration is that all the drugs routinely administered to individuals with Down syndrome do not necessarily have level I evidence from clinical trials performed in this population. This includes the recent COVID-19 vaccines that have preserved the lives of thousands of individuals with Down syndrome. Individuals with Down syndrome are known to have a 10-fold increased mortality rate due to COVID-19, and despite well-recognized differences in immunity and vaccine response, they benefited from treatment with the vaccine.<sup>7</sup> The expectation that all drugs approved for Alzheimer disease in the general population will have a clinical trial in persons with Down syndrome (even safety data) may be unrealistic and might preclude access to the growing number of treatments for Alzheimer disease. Conversely, bridging studies are imperative to ensure that life-saving amyloid-lowering therapies for Alzheimer disease are safe in this unique population.

Adults with Down syndrome–related Alzheimer disease, as well as those with autosomal-dominant Alzheimer disease, show a higher burden of amyloid angiopathy compared with adults with sporadic Alzheimer disease, which might put them at higher risk for adverse events related to ARIA. However, in the absence of data in adults with Down syndrome, this theoretical risk has not materialized so far in autosomal-dominant Alzheimer disease, in which the overall prevalence of ARIA of edema/effusions observed with gantenerumab was lower than that observed in clinical trials in sporadic Alzheimer disease.<sup>8</sup> Furthermore, apolipoprotein E  $\epsilon$ 4 carriers (particularly E4 homozygotes who also experience a much higher rate of ARIA) have not been excluded from access to studies or clinical use.

Ensuring equitable access should therefore be the priority, while balanced with safety. It is imperative that controlled data are acquired to estimate the safety of these medications without precluding access.

Beyond these challenges, Down syndrome offers unique opportunities for drug development. Disease-modifying treatments might be more effective if administered in the preclinical phase of the disease. However, proving clinical benefit in the general population in the preclinical phase is difficult due to the uncertainties of who will develop the disease and when, despite the use of biomarkers. The near full penetrance and a similar predictability of disease onset between Down syndrome–related Alzheimer disease and autosomal-dominant Alzheimer disease<sup>4,9</sup> could greatly facilitate preventive trials in this population. However, while the opportunity for performing such studies in autosomal-dominant Alzheimer disease has been long recognized, it has been long neglected in Down syndrome–related Alzheimer disease, and only recently have trials been planned. With more than 500 000 individuals with Down syndrome in the US and Europe alone, the opportunity to conduct primary and secondary trials is unparalleled.

People with Down syndrome have demonstrated their willingness to participate in clinical trials. Indeed, in the past 5 years, there have been significant advances in the understanding

of the natural history of Alzheimer disease in Down syndrome and in the constitution of several international consortia.<sup>3</sup> This is due, in no small part, to groundbreaking studies in the Down syndrome population such as the Alzheimer Biomarker Consortium – Down Syndrome (ABC-DS) and establishment of the Trial Ready Cohort – Down Syndrome (TRC-DS). Additionally, collaborative European efforts, such as the Down Alzheimer Barcelona Neuroimaging Initiative (DABNI) and Horizon 21, are also finding similar results, confirming that the trajectory of clinical and biomarker changes in adults with Down syndrome are strikingly similar to those observed in sporadic Alzheimer disease and autosomal-dominant Alzheimer disease. Most of these expert sites, including those in ABC-DS, TRC-DS, and the European networks, together comprise the Alzheimer Clinical Trials Consortium – Down syndrome (ACTC-DS) and are utilizing a single harmonized protocol translated into several languages. Ongoing work on the most recent revision to the National Institute on Aging Alzheimer’s Association (NIA-AA) biological ATN (amyloid tau neurodegeneration) framework based upon the key Alzheimer disease biomarkers for defining the Alzheimer disease continuum now includes Down syndrome–related Alzheimer disease. We have now reached an inflection point in the Alzheimer disease field where the biomarker similarities between sporadic Alzheimer disease and the genetic forms, including Down syndrome–related Alzheimer disease, are well characterized, and cohorts with thousands of individuals with Down syndrome are being observed, using harmonized protocols across the world.

In this era of diversity, equity, and inclusion, now is the time to bring these new, disease-modifying treatments to individuals who have been left behind for far too long. We would address an ethical imperative and take advantage of a unique opportunity to not only improve the lives of people with Down syndrome, but also those in the general population.

### Conflict of Interest Disclosures:

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