# Diagnostic and prognostic performance and longitudinal changes in plasma NfL concentrations in adults with Down syndrome: a cohort study

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## Summary:

**This is the first study to assess the prognostic performance of plasma NfL levels to track prodromal and Alzheimer's disease dementia in people with Down syndrome and to describe the longitudinal trajectory of plasma Neurofilament light chain (NfL), along the course of Alzheimer's disease in Down syndrome. In addition, this study confirms the good diagnostic performance of plasma NfL in an international multicentre sample.**

**Background:**
Adults with Down syndrome are at an ultra-high risk of developing symptoms of Alzheimer's disease, but diagnosis of Alzheimer's disease in this population is challenging. We aimed to validate the clinical utility of plasma NfL, a marker of neurodegeneration, for the diagnosis of symptomatic Alzheimer's disease in Down syndrome. We also assessed its prognostic value and studied the longitudinal changes of this marker along the disease.

**Methods:**
We did a multicentre cohort study, including adults with Down syndrome, recruited from six hospital and university medical centres in France, Germany, Spain, the UK and the USA, who had been assessed and followed up, and provided at least two plasma samples. Participants were classified by clinicians as asymptomatic (no clinical suspicion of Alzheimer's disease), prodromal Alzheimer's disease or Alzheimer's dementia. Participants who changed their diagnosis during the follow up were classified as progressors. Plasma NfL concentrations were determined using ultrasensitive technology (SIMOA).

**Main results:**
- Between 2010 and 2019, 608 samples from 236 people with Down syndrome (70% asymptomatic, 14% prodromal Alzheimer's disease, 12% Alzheimer's dementia) were collected. The mean follow-up was 3.6 years.
- Baseline plasma NfL concentrations accurately differentiated the asymptomatic group from the prodromal Alzheimer's disease group (Area Under the Curve= 0.83) and from the Alzheimer's dementia group (Area Under the Curve = 0.94).
- Plasma NfL concentrations showed an annual increase of 3% per year in the asymptomatic non-progressors group, 11.5% per year in the asymptomatic progressors group and 16% per year in the prodromal Alzheimer's disease progressors group.
- In participants with Alzheimer's dementia, NfL concentrations increased by a mean of 24.3%.

**Implications for people with DS:**
This multicentre study has immediate implications in clinical practice, as it shows the clinical utility of plasma NfL for the diagnosis and prognosis of symptomatic Alzheimer's disease in Down syndrome. In addition, the longitudinal trajectory of plasma NfL, with increasing rates of change along the course of the disease, enables its use as a theragnostic marker in clinical trials.

**Conclusions:**
Plasma NfL concentrations have excellent diagnostic and prognostic performance for symptomatic Alzheimer's disease in Down syndrome. The longitudinal trajectory of plasma NfL supports its use as a marker in clinical trials.

**Take home messages:**
Plasma NfL concentrations is a useful biomarker for diagnosing and tracking the progression of Alzheimer's disease in Down syndrome.

**References:**
Carmona-Iragui M*, Alcolea D*, Barroeta I, et al. Diagnostic and prognostic performance and longitudinal changes in plasma NfL chain concentrations in adults with Down syndrome: a cohort study. *Lancet Neurol.* 2021 Aug;20(8):605-614.