

Supplementary material

Supplementary references

- S1 Zetterberg H. Neurofilament Light: A Dynamic Cross-Disease Fluid Biomarker for Neurodegeneration. *Neuron*. 2016;91:1–3. doi:10.1016/j.neuron.2016.06.030
- S2 Yuan A, Rao M V., Veeranna, et al. Neurofilaments and neurofilament proteins in health and disease. *Cold Spring Harb Perspect Biol* 2017;9. doi:10.1101/cshperspect.a018309
- S3 Petzold A. Neurofilament phosphoforms: Surrogate markers for axonal injury, degeneration and loss. *J Neurol Sci* 2005;233:183–98. doi:10.1016/j.jns.2005.03.015
- S4 Norgren N, Rosengren L, Stigbrand T. Elevated neurofilament levels in neurological diseases. *Brain Res* 2003;987:25–31. doi:10.1016/S0006-8993(03)03219-0
- S5 Steinacker P, Feneberg E, Weishaupt J, et al. Neurofilaments in the diagnosis of motoneuron diseases: A prospective study on 455 patients. *J Neurol Neurosurg Psychiatry* 2016;87:12–20. doi:10.1136/jnnp-2015-311387
- S6 Gaiottino J, Norgren N, Dobson R, et al. Increased Neurofilament Light Chain Blood Levels in Neurodegenerative Neurological Diseases. *PLoS One* 2013;8. doi:10.1371/journal.pone.0075091
- S7 Lycke JN, Karlsson J-E, Andersen O, et al. Neurofilament protein in cerebrospinal fluid: a potential marker of activity in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1998;64:402–4. doi:10.1136/jnnp.64.3.402
- S8 Teunissen CE, Iacobaeus E, Khademi M, et al. Combination of CSF N-acetylaspartate and neurofilaments in multiple sclerosis. *Neurology* 2009;72:1322–9. doi:10.1212/WNL.0b013e3181a0fe3f

- S9 Novakova L, Zetterberg H, Sundström P, et al. Monitoring disease activity in multiple sclerosis using serum neurofilament light protein. *Neurology* 2017;89:2230–7.
doi:10.1212/WNL.0000000000004683
- S10 Wang H, Wang C, Qiu W, et al. Cerebrospinal fluid light and heavy neurofilaments in neuromyelitis optica. *Neurochem Int* 2013;63:805–8. doi:10.1016/j.neuint.2013.10.008
- S11 Jonsson M, Zetterberg H, van Straaten E, et al. Cerebrospinal fluid biomarkers of white matter lesions - cross-sectional results from the LADIS study. *Eur J Neurol* 2010;17:377–82.
doi:10.1111/j.1468-1331.2009.02808.x
- S12 Gattringer T, Pinter D, Enzinger C, et al. Serum neurofilament light is sensitive to active cerebral small vessel disease. *Neurology* 2017;89:2108–14.
doi:10.1212/WNL.0000000000004645
- S13 Preische O, Schultz SA, Apel A, et al. Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer’s disease. *Nat Med* 2019 2019;;1. doi:10.1038/s41591-018-0304-3
- S14 Weston PSJ, Poole T, Ryan NS, et al. Serum neurofilament light in familial Alzheimer disease: A marker of early neurodegeneration. *Neurology* 2017;89:2167–75.
doi:10.1212/WNL.0000000000004667
- S15 Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer’s disease. *Alzheimers Dement* 2018;14:535–62.
doi:10.1016/j.jalz.2018.02.018
- S16 Molinuevo JL, Ayton S, Batrla R, et al. Current state of Alzheimer’s fluid biomarkers. Springer Berlin Heidelberg 2018. doi:10.1007/s00401-018-1932-x
- S17 Vijverberg EGB, Dols A, Krudop WA, et al. Cerebrospinal fluid biomarker examination as a tool to discriminate behavioral variant frontotemporal dementia from primary psychiatric disorders. *Alzheimer’s Dement Diagnosis, Assess Dis Monit* 2017;7:99–106.
doi:10.1016/j.dadm.2017.01.009

- S18 Pijnenburg YAL, Verwey NA, van der Flier WM, et al. Discriminative and prognostic potential of cerebrospinal fluid phosphoTau/tau ratio and neurofilaments for frontotemporal dementia subtypes. *Alzheimer's Dement Diagnosis, Assess Dis Monit* 2015;1:505–12. doi:10.1016/j.dadm.2015.11.001
- S19 De Schaepdryver M, Jeromin A, Gille B, et al. Comparison of elevated phosphorylated neurofilament heavy chains in serum and cerebrospinal fluid of patients with amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 2018;89:367–73. doi:10.1136/jnnp-2017-316605
- S20 Brooks BR, Miller RG, Swash M, et al. El Escorial revisited: Revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* 2000;1:293–9. doi:10.1080/146608200300079536
- S21 Tullberg M, Rosengren L, Blomsterwall E, et al. CSF neurofilament and glial fibrillary acidic protein in normal pressure hydrocephalus. *Neurology* 1998;50:1122–7.
- S22 Constantinescu R, Romer M, Oakes D, et al. Levels of the light subunit of neurofilament triplet protein in cerebrospinal fluid in Huntington's disease. *Park Relat Disord* 2009;15:245–8. doi:10.1016/j.parkreldis.2008.05.012
- S23 Byrne LM, Rodrigues FB, Blennow K, et al. Neurofilament light protein in blood as a potential biomarker of neurodegeneration in Huntington's disease: a retrospective cohort analysis. *Lancet Neurol* 2017;16:601–9. doi:10.1016/S1474-4422(17)30124-2
- S24 Shahim P, Zetterberg H, Tegner Y, et al. Serum neurofilament light as a biomarker for mild traumatic brain injury in contact sports. *Neurology* 2017;88:1788–94. doi:10.1212/WNL.0000000000003912
- S25 Modvig S, Degn M, Sander B, et al. Cerebrospinal fluid neurofilament light chain levels predict visual outcome after optic neuritis. *Mult Scler* 2016;22:590–8. doi:10.1177/1352458515599074

- S26 Gossink FT, Dols A, Kerssens CJ, et al. Psychiatric diagnoses underlying the phenocopy syndrome of behavioural variant frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 2016;87:64–8. doi:10.1136/jnnp-2014-308284
- S27 Brettschneider J, Del Tredici K, Toledo JB, et al. Stages of pTDP-43 pathology in amyotrophic lateral sclerosis. *Ann Neurol* 2013;74:20–38. doi:10.1002/ana.23937
- S28 Boxer AL, Lang AE, Grossman M, et al. Davunetide in patients with progressive supranuclear palsy: a randomised, double-blind, placebo-controlled phase 2/3 trial. *Lancet Neurol* 2014;13:676–85. doi:10.1016/S1474-4422(14)70088-2
- S29 Johnson EB, Byrne LM, Gregory S, et al. Neurofilament light protein in blood predicts regional atrophy in Huntington disease. *Neurology* 2018;90:e717–23.
- S30 Neselius S, Brisby H, Marcusson J, et al. Neurological assessment and its relationship to CSF biomarkers in amateur boxers. *PLoS One* 2014;9:1–8.
doi:10.1371/journal.pone.0099870
- S31 Shahim P, Tegner Y, Gustafsson B, et al. Neurochemical aftermath of repetitive mild traumatic brain injury. *JAMA Neurol* 2016;73:1308–15. doi:10.1001/jamaneurol.2016.2038
- S32 Novakova L, Axelsson M, Khademi M, et al. Cerebrospinal fluid biomarkers as a measure of disease activity and treatment efficacy in relapsing-remitting multiple sclerosis. *J Neurochem* 2017;141:296–304. doi:10.1111/jnc.13881
- S33 Kuhle J, Disanto G, Lorscheider J, et al. Fingolimod and CSF neurofilament light chain levels in relapsing-remitting multiple sclerosis. *Neurology* 2015;84:1639–43.
doi:10.1212/WNL.0000000000001491
- S34 Piehl F, Kockum I, Khademi M, et al. Plasma neurofilament light chain levels in patients with MS switching from injectable therapies to fingolimod. *Mult Scler J* 2017;:135245851771513. doi:10.1177/1352458517715132

- S35 Malmeström C, Haghighi S, Rosengren L, et al. Neurofilament light protein and glial fibrillary acidic protein as biological markers in MS. *Neurology* 2003;61:1720–5.
doi:10.1212/WNL.63.3.599
- S36 Gaetani L, Höglund K, Parnetti L, et al. A new enzyme-linked immunosorbent assay for neurofilament light in cerebrospinal fluid: analytical validation and clinical evaluation. *Alzheimers Res Ther* 2018;10:8. doi:10.1186/s13195-018-0339-1
- S37 Zetterberg H, Skillbäck T, Mattsson N, et al. Association of cerebrospinal fluid neurofilament light concentration with Alzheimer disease progression. *JAMA Neurol* 2016;73:60–7. doi:10.1001/jamaneurol.2015.3037
- S38 Hampel H, Toschi N, Baldacci F, et al. Alzheimer’s disease biomarker-guided diagnostic workflow using the added value of six combined cerebrospinal fluid candidates: A β 1–42 , total-tau, phosphorylated-tau, NFL, neurogranin, and YKL-40. *Alzheimer’s Dement* 2018;:1–10. doi:10.1016/j.jalz.2017.11.015
- S39 Pijnenburg YAL, Janssen JC, Schoonenboom NSM, et al. CSF neurofilaments in frontotemporal dementia compared with early onset Alzheimer’s disease and controls. *Dement Geriatr Cogn Disord* 2007;23:225–30. doi:10.1159/000099473
- S40 Goossens J, Bjerke M, Van Mossevelde S, et al. Diagnostic value of cerebrospinal fluid tau, neurofilament, and progranulin in definite frontotemporal lobar degeneration. *Alzheimers Res Ther* 2018;10:31. doi:10.1186/s13195-018-0364-0
- S41 Meeter LH, Doppert EG, Jiskoot LC, et al. Neurofilament light chain: a biomarker for genetic frontotemporal dementia. *Ann Clin Transl Neurol* 2016;3:623–36.
doi:10.1002/acn3.325
- S42 Landqvist Waldö M, Frizell Santillo A, Passant U, et al. Cerebrospinal fluid neurofilament light chain protein levels in subtypes of frontotemporal dementia. *BMC Neurol* 2013;13:1–8. doi:10.1186/1471-2377-13-54

- S43 Scherling CS, Hall T, Berisha F, et al. Cerebrospinal fluid neurofilament concentration reflects disease severity in frontotemporal degeneration. *Ann Neurol* 2014;75:116–26. doi:10.1002/ana.24052
- S44 Zetterberg H, Jacobsson J, Rosengren L, et al. Cerebrospinal fluid neurofilament light levels in amyotrophic lateral sclerosis: Impact of SOD1 genotype. *Eur J Neurol* 2007;14:1329–33. doi:10.1111/j.1468-1331.2007.01972.x
- S45 Menke RAL, Gray E, Lu CH, et al. CSF neurofilament light chain reflects corticospinal tract degeneration in ALS. *Ann Clin Transl Neurol* 2015;2:748–55. doi:10.1002/acn3.212
- S46 Hall S, Surova Y, Öhrfelt A, et al. CSF biomarkers and clinical progression of Parkinson disease. *Neurology* 2015;84:57–63. doi:10.1212/WNL.0000000000001098
- S47 Hansson O, Janelidze S, Hall S, et al. Blood-based NfL: A biomarker for differential diagnosis of parkinsonian disorder. *Neurology* 2017;88:930–7. doi:10.1212/WNL.0000000000003680
- S48 Yilmaz A, Blennow K, Hagberg L, et al. Neurofilament light chain protein as a marker of neuronal injury: review of its use in HIV-1 infection and reference values for HIV-negative controls. *Expert Rev Mol Diagn* 2017;17:761–70. doi:10.1080/14737159.2017.1341313
- S49 Petzold A, Keir G, Warren J, et al. A systematic review and meta-analysis of CSF neurofilament protein levels as biomarkers in dementia. *Neurodegener Dis* 2007;4:185–94. doi:10.1159/000101843
- S50 Petzold A, Altintas A, Andreoni L, et al. Neurofilament ELISA validation. *J Immunol Methods* 2010;352:23–31. doi:10.1016/j.jim.2009.09.014
- S51 Rissin DM, Kan CW, Campbell TG, et al. Single-molecule enzyme-linked immunosorbent assay detects serum proteins at subfemtomolar concentrations. *Nat Biotechnol* 2010;28:595–9. doi:10.1038/nbt.1641

- S52 Gisslén M, Price RW, Andreasson U, et al. EBioMedicine Plasma Concentration of the Neurofilament Light Protein (NFL) is a Biomarker of CNS Injury in HIV Infection : A Cross-Sectional Study. *EBIOM* 2016;3:135–40. doi:10.1016/j.ebiom.2015.11.036
- S53 Hansson O, Janelidze S, Hall S, et al. Blood-based NfL: A biomarker for differential diagnosis of parkinsonian disorder. *Neurology* 2017;88:930–7. doi:10.1212/WNL.0000000000003680

References used to generate Figure 2

- 1 Anesten B, Yilmaz A, Hagberg L, et al. Blood-brain barrier integrity, intrathecal immunoactivation, and neuronal injury in HIV. *Neurol Neuroimmunol NeuroInflammation* 2016;3:1–7. doi:10.1212/NXI.0000000000000300
- 2 Abdulle S, Mellgren Å, Brew BJ, et al. CSF neurofilament protein (NFL) - A marker of active HIV-related neurodegeneration. *J Neurol* 2007;254:1026–32. doi:10.1007/s00415-006-0481-8
- 3 Abu-Rumeileh S, Capellari S, Stanzani-Maserati M, et al. The CSF neurofilament light signature in rapidly progressive neurodegenerative dementias. *Alzheimer's Res Ther* 2018;10:1–11. doi:10.1186/s13195-017-0331-1
- 4 Steinacker P, Blennow K, Halbgebauer S, et al. Neurofilaments in blood and CSF for diagnosis and prediction of onset in Creutzfeldt-Jakob disease. *Sci Rep* 2016;6:1–6. doi:10.1038/srep38737
- 5 Van Eijk JJJ, Van Everbroeck B, Abdo WF, et al. CSF neurofilament proteins levels are elevated in sporadic Creutzfeldt-Jakob disease. *J Alzheimer's Dis* 2010;21:569–76. doi:10.3233/JAD-2010-090649
- 6 Jeppsson A, Höltta M, Zetterberg H, et al. Amyloid mis-metabolism in idiopathic normal pressure hydrocephalus. *Fluids Barriers CNS* 2016;13:1–7. doi:10.1186/s12987-016-0037-y

- 7 Jeppsson A, Zetterberg H, Blennow K, et al. Idiopathic normal-pressure hydrocephalus: pathophysiology and diagnosis by CSF biomarkers. *Neurology* 2013;80:1385–92. doi:10.1212/WNL.0b013e31828c2fda
- 8 Ågren-Wilsson A, Lekman A, Sjöberg W, et al. CSF biomarkers in the evaluation of idiopathic normal pressure hydrocephalus. *Acta Neurol Scand* 2007;116:333–9. doi:10.1111/j.1600-0404.2007.00890.x
- 9 Tullberg M, Rosengren L, Blomsterwall E, et al. CSF neurofilament and glial fibrillary acidic protein in normal pressure hydrocephalus. *Neurology* 1998;50:1122–7.
- 10 Kuhle J, Plattner K, Bestwick JP, et al. A comparative study of CSF neurofilament light and heavy chain protein in MS. *Mult Scler* 2013;19:1597–603. doi:10.1177/1352458513482374
- 11 Hakansson I, Tisell A, Cassel P, et al. Neurofilament light chain in cerebrospinal fluid and prediction of disease activity in clinically isolated syndrome and relapsing remitting multiple sclerosis. *Eur J Neurol* 2017;24:703–12. doi:10.1111/ene.13274
- 12 Novakova L, Axelsson M, Khademi M, et al. Cerebrospinal fluid biomarkers as a measure of disease activity and treatment efficacy in relapsing-remitting multiple sclerosis. *J Neurochem* 2017;141:296–304. doi:10.1111/jnc.13881
- 13 van der Vuurst de Vries RM, Wong YYM, Mescheriakova JY, et al. High neurofilament levels are associated with clinically definite multiple sclerosis in children and adults with clinically isolated syndrome. *Mult Scler* 2018;:1352458518775303. doi:10.1177/1352458518775303
- 14 Shahim P, Tegner Y, Gustafsson B, et al. Neurochemical aftermath of repetitive mild traumatic brain injury. *JAMA Neurol* 2016;73:1308–15. doi:10.1001/jamaneurol.2016.2038
- 15 Neselius S, Brisby H, Theodorsson A, et al. Csf-biomarkers in olympic boxing: Diagnosis and effects of repetitive head trauma. *PLoS One* 2012;7:1–8. doi:10.1371/journal.pone.0033606

- 16 Van Geel WJA, Rosengren LE, Verbeek MM. An enzyme immunoassay to quantify neurofilament light chain in cerebrospinal fluid. *J Immunol Methods* 2005;296:179–85. doi:10.1016/j.jim.2004.11.015
- 17 Hall S, Öhrfelt A, Constantinescu R, et al. Accuracy of a panel of 5 cerebrospinal fluid biomarkers in the differential diagnosis of patients with dementia and/or Parkinsonian disorders. *Arch Neurol* 2012;69:1445–52. doi:10.1001/archneurol.2012.1654
- 18 Magdalinou NK, Paterson RW, Schott JM, et al. A panel of nine cerebrospinal fluid biomarkers may identify patients with atypical parkinsonian syndromes. *J Neurol Neurosurg Psychiatry* 2015;86:1240–7. doi:10.1136/jnnp-2014-309562
- 19 Hall S, Surova Y, Öhrfelt A, et al. Longitudinal Measurements of Cerebrospinal Fluid Biomarkers in Parkinson’s Disease. *Mov Disord* 2016;31:898–905. doi:10.1002/mds.26578
- 20 Herbert MK, Aerts MB, Beenes M, et al. CSF neurofilament light chain but not FLT3 ligand discriminates parkinsonian disorders. *Front Neurol* 2015;6:1–7. doi:10.3389/fneur.2015.00091
- 21 Bäckström DC, Domellöf ME, Linder J, et al. Cerebrospinal fluid patterns and the risk of future dementia in early, incident Parkinson disease. *JAMA Neurol* 2015;72:1175–82. doi:10.1001/jamaneurol.2015.1449
- 22 Hall S, Surova Y, Öhrfelt A, et al. CSF biomarkers and clinical progression of Parkinson disease. *Neurology* 2015;84:57–63. doi:10.1212/WNL.0000000000001098
- 23 De Jong D, Jansen RWMM, Pijnenburg YAL, et al. CSF neurofilament proteins in the differential diagnosis of dementia. *J Neurol Neurosurg Psychiatry* 2007;78:936–8. doi:10.1136/jnnp.2006.107326
- 24 Pijnenburg YAL, Janssen JC, Schoonenboom NSM, et al. CSF neurofilaments in frontotemporal dementia compared with early onset Alzheimer’s disease and controls. *Dement Geriatr Cogn Disord* 2007;23:225–30. doi:10.1159/000099473

- 25 Landqvist Waldö M, Frizell Santillo A, Passant U, et al. Cerebrospinal fluid neurofilament light chain protein levels in subtypes of frontotemporal dementia. *BMC Neurol* 2013;13:1–8. doi:10.1186/1471-2377-13-54
- 26 Skillback T, Farahmand B, Bartlett JW, et al. CSF neurofilament light differs in neurodegenerative diseases and predicts severity and survival. *Neurology* 2014;83:1945–53. doi:10.1212/WNL.0000000000001015
- 27 Zetterberg H, Skillbäck T, Mattsson N, et al. Association of cerebrospinal fluid neurofilament light concentration with Alzheimer disease progression. *JAMA Neurol* 2016;73:60–7. doi:10.1001/jamaneurol.2015.3037
- 28 Alcolea D, Vilaplana E, Suárez-Calvet M, et al. CSF sAPP β , YKL-40, and neurofilament light in frontotemporal lobar degeneration. *Neurology* 2017;89:178–88. doi:10.1212/WNL.0000000000004088
- 29 Lista S, Toschi N, Baldacci F, et al. Diagnostic accuracy of CSF neurofilament light chain protein in the biomarker-guided classification system for Alzheimer’s disease. *Neurochem Int* 2017;108:355–60. doi:10.1016/j.neuint.2017.05.010
- 30 Hampel H, Toschi N, Baldacci F, et al. Alzheimer’s disease biomarker-guided diagnostic workflow using the added value of six combined cerebrospinal fluid candidates: A β 1–42 , total-tau, phosphorylated-tau, NFL, neurogranin, and YKL-40. *Alzheimer’s Dement* 2018;:1–10. doi:10.1016/j.jalz.2017.11.015
- 31 Paterson RW, Slattery CF, Poole T, et al. Cerebrospinal fluid in the differential diagnosis of Alzheimer’s disease: Clinical utility of an extended panel of biomarkers in a specialist cognitive clinic. *Alzheimer’s Res Ther* 2018;10:1–11. doi:10.1186/s13195-018-0361-3
- 32 Goossens J, Bjerke M, Van Mossevelde S, et al. Diagnostic value of cerebrospinal fluid tau, neurofilament, and progranulin in definite frontotemporal lobar degeneration. *Alzheimers Res Ther* 2018;10:31. doi:10.1186/s13195-018-0364-0

- 33 Steinacker P, Huss A, Mayer B, et al. Diagnostic and prognostic significance of neurofilament light chain NF-L, but not progranulin and S100B, in the course of amyotrophic lateral sclerosis: Data from the German MND-net. *Amyotroph Lateral Scler Front Degener* 2017;18:112–9. doi:10.1080/21678421.2016.1241279
- 34 Oeckl P, Jardel C, Salachas F, et al. Multicenter validation of CSF neurofilaments as diagnostic biomarkers for ALS. *Amyotroph Lateral Scler Front Degener* 2016;17:404–13. doi:10.3109/21678421.2016.1167913
- 35 Lu C-H, Macdonald-Wallis C, Gray E, et al. Neurofilament light chain: A prognostic biomarker in amyotrophic lateral sclerosis. *Neurology* 2015;84:2247–57. doi:10.1212/WNL.0000000000001642
- 36 Menke RAL, Gray E, Lu CH, et al. CSF neurofilament light chain reflects corticospinal tract degeneration in ALS. *Ann Clin Transl Neurol* 2015;2:748–55. doi:10.1002/acn3.212
- 37 Zetterberg H, Jacobsson J, Rosengren L, et al. Cerebrospinal fluid neurofilament light levels in amyotrophic lateral sclerosis: Impact of SOD1 genotype. *Eur J Neurol* 2007;14:1329–33. doi:10.1111/j.1468-1331.2007.01972.x
- 38 Meeter LHH, Vijverberg EG, Del Campo M, et al. Clinical value of neurofilament and phospho-tau/tau ratio in the frontotemporal dementia spectrum. *Neurology* 2018;90:e1231–9. doi:10.1212/WNL.0000000000005261
- 39 Constantinescu R, Rosengren L, Johnels B, et al. Consecutive analyses of cerebrospinal fluid axonal and glial markers in Parkinson’s disease and atypical parkinsonian disorders. *Park Relat Disord* 2010;16:142–5. doi:10.1016/j.parkreldis.2009.07.007
- 40 Abdo WF, Bloem BR, Van Geel WJ, et al. CSF neurofilament light chain and tau differentiate multiple system atrophy from Parkinson’s disease. *Neurobiol Aging* 2007;28:742–7. doi:10.1016/j.neurobiolaging.2006.03.010

41 Abdo WF, Van De Warrenburg BPC, Munneke M, et al. CSF analysis differentiates multiple-system atrophy from idiopathic late-onset cerebellar ataxia. *Neurology* 2006;67:474–9. doi:10.1212/01.wnl.0000227891.25592.8c