Accuracy of blood-based neurofilament light to different genetic frontotemporal dementia from primary psychiatric disorders

Ella Liu[1] (iD), Sherri Lee Jones[2] (iD), Victoria Light[3] (iD), Charlotte Teunissen[3] (iD),
Arabella Bouzigues[4] (iD), Lucy L Russell[4] (iD), Phoebe H Foster[4] (iD), Eve Ferry-Bolder[4] (iD),
John C van Swieten[5], Lize C Jiskoot[5], Harro Seelaar[5] (iD), Raquel Sanchez-Valle[6],
Robert Laforce[7] (iD), Caroline Graff[8] (iD), Daniela Galimberti[9] (iD), Rik Vandenberghe[10] (iD),
Alexandre de Mendonça[11] (iD), Pietro Tiraboschi[12], Isabel Santana[13] (iD),
Alexander Gerhard[14,15,16] (iD), Johannes Levin[17,18,19] (iD), Sandro Sorbi[20], Markus Otto[21],
Chris R Butler[22], Isabelle Le Ber[23] (iD), Elizabeth Finger[24], Maria Carmela Tartaglia[25] (iD),
Mario Masellis[26], James B Rowe[27], Matthis Synofzik[28] (iD), Fermin Moreno[29] (iD),
Barbara Borroni[30] (iD), Henrik Zetterberg[31] (iD), Jonathan D Rohrer[4],
Simon Ducharme[2,32] (iD) and on behalf of the Genetic Frontotemporal Dementia
Initiative (GENFI) and Banque Signature (BbS)

[1]Department of Anatomy and Cell Biology, McGill University, Montréal, Québec, Canada
[2]Douglas Mental Health University Institute, Department of Psychiatry, McGill University, Verdun, Québec, Canada
[3]Amsterdam Neurochemistry Laboratory, Department of Laboratory Medicine, Amsterdam Neuroscience, Neurodegeneration, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, North Holland, Netherlands
[4]Dementia Research Centre, Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, London, Greater London, UK
[5]Department of Neurology, Erasmus Medical Centre, Rotterdam, South Holland, Netherlands
[6]Alzheimer's Disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic, Institut d'Investigacións Biomèdiques August Pi I Sunyer, University of Barcelona, Barcelona, Catalonia, Spain
[7]Clinique Interdisciplinaire de Mémoire, Département des Sciences Neurologiques, CHU de Québec, and Faculté de Médecine, Université Laval, Québec, Canada
[8]Department of Neurobiology, Care Sciences and Society, Center for Alzheimer Research, Division of Neurogeriatrics, Bioclinicum, Karolinska Institutet, Huddinge, Södermanland, Sweden
[9]Fondazione Ca' Granda, IRCCS Ospedale Policlinico, Milano, Milano, Italy
[10]Laboratory for Cognitive Neurology, Department of Neurosciences, KU Leuven, Campus O&N II, Leuven, Flemish Brabant, Belgium
[11]Faculty of Medicine, University of Lisbon, Lisboa, Lisbon, Portugal
[12]Department of Neurology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Milano, Italy
[13]University Hospital of Coimbra (HUC), Neurology Service, Faculty of Medicine, University of Coimbra, Coimbra, Beira Litoral, Portugal
[14]Division of Psychology Communication and Human Neuroscience, Wolfson Molecular Imaging Centre, University of Manchester, Withington, Manchester, Greater Manchester, UK
[15]Department of Nuclear Medicine, Center for Translational Neuro- and Behavioral Sciences, University Hospital Essen, Essen, North Rhine-Westphalia, Germany

[16]Department of Geriatric Medicine, Klinikum Hochsauerland, Arnsberg, North Rhine-Westphalia, Germany
[17]Department of Neurology, LMU University Hospital, LMU Munich, München, Bavaria, Germany
[18]Germany Center for Neurodegenerative Diseases, site Munich, München, Bavaria, Germany
[19]Department of Neurology, Munich Cluster for Systems Neurology (SyNergy), München, Bavaria, Germany
[20]Department of Neurofarba, University of Florence, Florence, Florence, Italy
[21]Department of Neurology, University of Ulm, Ulm, Baden-Württemberg, Germany
[22]Nuffield Department of Clinical Neurosciences, Medical Sciences Division, University of Oxford, Oxford, Oxfordshire, UK
[23]Sorbonne Université, Paris Brain Institute – Institut du Cerveau – ICM, Hôpital Pitié, Paris, Île-de-France, France
[24]Department of Clinical Neurological Sciences, London Health Sciences Centre, University Hospital, University of Western Ontario, London, Ontario, Canada
[25]Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Medical Sciences Building, Toronto, Ontario, Canada
[26]Sunnybrook Health Sciences Centre, Sunnybrook Research Institute, University of Toronto, Toronto, Ontario, Canada
[27]Department of Clinical Neurosciences, Cambridge University Hospitals NHS Trust, and MRC Cognition and Brain Sciences Unit, University of Cambridge, Cambridge, Cambridgeshire, UK
[28]Department of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research and Center of Neurology, University of Tübingen, Tübingen, Baden-Württemberg, Germany
[29]Cognitive Disorders Unit, Department of Neurology, Donostia Universitary Hospital, Donostia-San Sebastiàn, Gipuzkoa, Spain
[30]Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Brescia, Italy

Abstract

Background: Genetic frontotemporal dementia (FTD) along with Alzheimer's disease (AD), is one of the most prevalent early-onset dementias. The differential diagnosis of FTD from primary psychiatric disorder (PPD) has been challenging due to significant symptom overlap, particular as FTD often presents with prolonged psychiatric prodromes.

Objective: This study aims to evaluate whether blood-based neurofilament light chain (NfL) can differentiate genetic FTD from PPD, and to determine a global clinical cutoff to differentiate genetic FTD carriers from PPD with high specificity and sensitivity.

Methods: Data (ages 40–81) were obtained from FTD mutation carriers (GENFI; $n = 474$; $n = 120$ *C9orf72*, $n = 114$ *GRN*, $n = 50$ *MAPT*, $n = 190$ controls), and PPD (Biobanque Signature; $n = 848$). Blood-based NfL was measured with SIMOA HD-X (BbS) and SIMOA HD-1 (GENFI).

Results: Blood-based NfL was higher in all symptomatic mutations compared to PPD. Mildly symptomatic (0 < FTLD CDR-SOB-NM < 4) *C9orf72* and *GRN* carriers also had higher NfL. ROC curve revealed an optimal blood-based NfL cutoff of 22.1 pg/mL ($J = 0.647$) to distinguish symptomatic genetic FTD from PPD (78.5% sensitivity, 86.2% specificity, AUC = 0.908). For mildly symptomatic subjects, a cutoff of 16.2 pg/mL ($J = 0.601$) differentiated groups with 86.7% sensitivity and 73.5% specificity (AUC = 0.870).

Conclusions: NfL holds potential as a blood-based biomarker for symptomatic genetic FTD carriers, with moderate accuracy to distinguish PPD from mild forms including *C9orf72*.

Introduction

Genetic frontotemporal dementia (FTD) has heterogenous clinical presentations for each of the common causal mutations: repeat expansion in chromosome 9 open reading frame 72 (*C9orf72*), mutations in progranulin (*GRN*) and microtubule-associated protein tau (*MAPT*).[1] The most common presentation is the behavioral variant of FTD (bvFTD) which is challenging to identify clinically in the early stages due to the nature of behavioral symptoms at onset which strongly overlap those of primary psychiatric disorders (PPD).[2] Further, these patients (in particular *C9orf72* and *GRN* carriers) can have protracted psychiatric prodromes before exhibiting more specific FTD features, exacerbating diagnostic confusion.[3,4] There is a need for a simple biomarker that could differentiate PPD from early stage FTD in order to direct patients toward relevant genetic testing and appropriate care.

Neurofilament light chain (NfL) is a structural axonal protein that is released from physiologic turnover and neuronal damage.[5,6] NfL increases sharply in patients with neurodegenerative diseases. It also increases slowly with age, with a more pronounced increase after the ages of 60–70.[6–8] However, unlike bvFTD, PPD is not associated with overt neuronal damage.[9–11] Therefore, blood-based (serum and plasma) NfL is emerging as a candidate biomarker to differentiate bvFTD (high levels) from PPD (normal to mildly elevated levels).[9,12,13] In the study with the largest sample size so far, we previously reported that PPD can be distinguished from bvFTD (primarily sporadic) with serum NfL cutoffs of 17.0 pg/mL with good accuracy (82.9% sensitivity, 76.1% specificity, AUC = 0.847).[14] However, there is currently a lack of studies investigating the use of blood-based NfL as a biomarker to differentiate various disease stages of genetic FTD from PPD.[15] In particular, it is crucial to determine if blood- NfL can differentiate prodromal forms of FTD due to *C9orf72*, which often presents with marked psychiatric symptoms, including psychosis.[4]

Recent findings have shown that carriers of all three mutation groups have increased blood-based NfL after symptom onset, but with differences in the genotype-based pattern of NfL elevation.[16,17] In *C9orf72*, blood-based NfL levels slowly and steadily rise over noncarrier controls early

[31]UK Dementia Research Institute, Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, London, Greater London, UK

[32]McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montréal, Québec, Canada

Corresponding author:
Simon Ducharme, Douglas Mental Health University Institute, Department of Psychiatry, McGill University, 6875 boulevard LaSalle, Verdun, H4H 1R3 Québec, Canada.
Email: simon.ducharme@mcgill.ca

on, around 30 years before symptom onset, and remained elevated throughout the presymptomatic period. In *GRN,* blood-based NfL levels start to rise over controls 15 years before symptom onset and continue rising, with fastest elevation during late presymptomatic stages, near symptom onset. In *MAPT,* however, blood-based NfL levels were not elevated during the presymptomatic stages and only started to rise at symptom onset, remaining significantly increased throughout the symptomatic phase of disease.

The overarching goals of this study are to evaluate blood-based (serum and plasma) NfL as a biomarker to differentiate PPD from symptomatic and prodromal genetic FTD in *C9orf72*, *GRN,* and *MAPT* mutation carrier and to identify the best potential cutoff for this purpose. We hypothesize that 1) in symptomatic FTD genetic mutation carriers, plasma NfL will be higher than serum NfL in PPD; 2a) in comparison to serum NfL levels in PPD, higher plasma NfL levels will be found in late presymptomatic and mildly symptomatic genetic mutation carriers within ten years of estimated onset 2b) that this effect would be strongest in late presymptomatic *C9orf72* mutation carriers; 3) in noncarrier controls, plasma NfL will be similar to PPD; 4) global clinical cutoffs will be able to differentiate genetic FTD mutation carriers from PPD with high specificity and sensitivity.

Methods

Participants: Genetic Frontotemporal Initiative (GENFI)

Participant data ($n = 1130$) was acquired from Genetic Frontotemporal Initiative 1 (GENFI1) and Genetic Frontotemporal Initiative 2 (GENFI2) (combined in data freeze six). The subjects of the study were confirmed symptomatic FTD with a genetic mutation in *C9orf72*, *GRN,* or *MAPT* and their at-risk presymptomatic first-degree relatives.[18] The first-degree relatives were further subdivided into healthy noncarriers ($n = 190$), serving as controls and late presymptomatic mutation carriers.[18] Participants underwent annual comprehensive assessment including neurological and neuropsychological examinations, blood collection, and brain imaging.[18] Only participants aged 40 or older were included, as this is the typical age of FTD onset and to match the psychiatric cohort. The symptomatic genetic mutation carriers were identified clinically and classified by expert clinicians into their respective diagnoses according to previously established diagnostic criteria for FTD subtypes.[18–20] The score used to estimate disease severity in this study was the FTLD-CDR-SOB-NM, which is the Sum of Boxes (SOB) of the FTLD modules plus the algorithm derived neuropsychiatric (N) scores, which uses the same scoring system as the Clinical Dementia Rating scale (CDR), but also factor in visual

hallucinations, auditory hallucination, and delusions.[21] It also includes a clinical judgment motor score (M) to capture the full picture of prodromal FTD stages.[22] In our study, the late presymptomatic group comprised patients who were clinically asymptomatic at the time of measurement but were within 10 years or less of their estimated years of onset (EYO). The estimated years of onset for late presymptomatic genetic FTD carriers was based on the mean age of onset of the participant's family.[23] The same classification was used for all mutations. The mildly symptomatic group for our study were the identified symptomatic mutation carriers classified as having a FTLD-CDR-SOB-NM score greater than 0 and less than 4 (approximately equivalent to a global score of 0.5). Only symptomatic, late presymptomatic (EYO ≥ -10), and mildly symptomatic genetic FTD carriers with at least one plasma NfL measurement were included, giving a total of 284 GENFI genetic FTD mutation carriers (120 *C9orf72,* 114 *GRN*, and 50 *MAPT* carriers) and 190 GENFI noncarrier controls. For each participant we used the latest visit at which a plasma NfL measurement was available and coinciding clinical data.

Each research center in the GENFI study received approval from their local ethics committees prior to the start of the review.[18] Moreover, all participants provided written informed consent per the *Declaration of Helsinki* prior to enrolment in the study.[18] This project was approved by the McGill University Health Center's Research Ethics Board.

Participants: Banque Signature (BbS)

Data from subjects with primary psychiatric disorders (PPD) aged 40–81, were obtained from the *Banque Signature* (BbS) of the *Institut Universitaire en Santé Mentale de Montréal (IUSMM)*.[24] Subjects from the psychiatric emergency department of the IUSMM had biospecimen samples collected in the morning after an overnight fast by trained research nurses.[24,25] Psychiatric disorders were established clinically by treating psychiatrists at longitudinal follow-up based on clinical criteria.[24] The patient diagnoses were coded following the *World Health International Classification of Disease* (ICD-10).[25] Consistent with the literature, psychiatric disorder comorbidity was common, with some patients receiving up to four different diagnoses.[24] For this study, the patients were categorized based on their primary psychiatric disorder diagnosis, consisting of substance use ($n = 61$), psychosis ($n = 268$), mood ($n = 285$), anxiety ($n = 142$), personality ($n = 78$), and other psychiatric disorders ($n = 14$), which included symptomatic participants who did not fit into the other diagnostic categories. All participants signed an informed consent form and the Banque Signature received approval from the local scientific evaluation and research ethics committees of the

Louis-H. Lafontain Hospital (renamed in March 2013 as CER-CEMTL) following the *Declaration of Helsinki*.[24]

The BbS participants who were healthy controls or with no identified psychiatric disorder at follow-up were not included in the analyses ($n = 70$). Exclusion criteria also included participants that had a neurocognitive disorder or delirium in their primary or secondary diagnosis ($n = 10$); and participants with advanced kidney disease (a factor known to significantly increase NfL $-n = 13$). Moreover, PPD patients missing a serum NfL measurement were excluded ($n = 2$), giving a total of 848 BbS subjects for analyses.

Serum NfL quantification (BbS)

Serum samples from BbS were collected and sent on a refrigerated block (4°C) to the VUMC location of the Neurochemistry Lab at AUMC (Head: Teunissen) for further analysis which occurred within 2 h of reception, with no freeze-thaw cycles required. Established Standard Operating Procedures (SOPs) and Good Clinical Practice (GCP) guidelines were adhered when transporting bio samples. At a single site, serum samples from BbS were measured following the manufacturer's instructions for their levels of NfL using a 4-plex NfL assay with the single molecule array (Simoa) technique and the SIMOA HD-X Analyzer (Quanterix, Billerica, MA, USA). The BbS study period in which the samples were collected ran from December 2012 to March 2020. The consistency between different assays was assessed using three internal quality control samples with concentrations of 111.6, 26.4, and 11.8 pg/mL, in which the values matched those observed in previous AUMC FTD sample analyses. All serum NfL levels were reported as mean ± standard deviation (SD) in pg/mL.

Plasma NfL quantification (GENFI2)

Plasma samples from GENFI were collected, processed, and stored at −80 °C following standard procedures within 24 h of collection.[26] For measurements, the samples were thawed at room temperature for 2 h then centrifuged for 5 min, with no more than one freeze-thaw cycle. The resulting samples were aliquoted into 150 µL, plated into 96-well plates, and frozen at −80°C until analysis. Measurements were done at a single site using the SIMOA HD-1 Analyzer (UCL, London) and a 1-plex NfL assay was conducted. The majority of sNFL data was analyzed in a single batch. However, some additional data was incorporate through two subsequent analyses likely conducted across three timepoints between 2019 and 2022. The total GENFI study period in which data was collected was from 2012 to 2022. Quality control samples showed

an intra-assay and inter-assay coefficient of variation with a mean value of 4.3%. All the plasma NfL values were displayed as mean ± standard deviation (SD) in pg/mL

Although plasma NfL values were obtained from GENFI and serum NfL from BbS, previous studies reported the two to be comparable, allowing for their comparison in our analyses.[27,28] The 4-plex NfL assay used in BbS and the 1-plex NfL assay used in GENFI have been shown to have strong positive and linear relationships between the two assays (correlation coefficients > 0.95). However, internal data showed 1.1- to 1.4-fold higher NfL concentrations by 4-plex compared with 1-plex. Therefore, a sensitivity analysis factorizing the 1-plex GENFI concentrations with 1.25 (mean between 1.1 and 1.4) was conducted on all main analyses to compare with the results obtained using the uncorrected pooled data.

Statistical analyses

Statistical analyses were done using IBM SPSS Statistics V.29.0.0.0. The significance level was set at an $\alpha = 0.05$ (2-tailed).

The statistical assumptions were verified prior to running analyses. The distribution of plasma NfL data from GENFI and serum NfL from PPD participants was log-transformed to normalize the data. Assumptions of the homogeneity of variance of all samples were tested using Levene's Test for Equality of Variances. Although Levene's test was violated for homoscedasticity in log blood-based NfL levels between genetic FTD and PPD groups, in accordance with the central limit theorem, the general linear models (GLM) used in this study were robust against these violations due to the large GENFI ($n = 269$) and PPD ($n = 848$) sample sizes.[29]

Previous studies reported that blood-based NfL levels increase with age.[6,30–32] Furthermore, there has been conflicting findings in literature regarding sex differences in blood-based NfL, with some studies finding no distinctions and others reported a difference.[33–36] Therefore, to assess the effects of these variables on blood-based NfL, first we conducted a bivariate Pearson's correlation test to determine the association between blood-based NfL level and age of our entire cohort (comprising FTD and PPD participants). Second, we conducted an independent sample t-test between all males and female participants of the study (FTD and PPD combined) to determine potential sex differences in blood-based NfL levels within our cohort.

To investigate whether blood-based log NfL levels differed in symptomatic, late presymptomatic, and the subgroup of mildly symptomatic genetic FTD *C9orf72, GRN*, and *MAPT* carriers as well as noncarriers controls, in comparison to individuals with PPD, we conducted general linear models. In these analyses age was included as a covariate as we reported a positive correlation between age and

blood-based NfL ($r = 0.346$, $p < 0.001$). In addition, although our analyses did not reveal a difference in blood-based NfL levels between males and females, we included sex as a covariate due to mixed results reported in previous studies.[33–36] Consequently, in accordance with established guidelines for sex and gender equity in research, the interaction between sex and group was entered in all analyses and are reported in results.[37] We used partial eta squared (η_p^2) and Cohen's *d* calculated with estimated marginal means to report effect size. The statistical significance was set at an $\alpha = 0.05$. We investigated four level of contrasts: 1) Symptomatic FTD versus PPD, 2) Late presymptomatic FTD within 10 years or less of their estimated years of onset versus PPD, 3) Mildly symptomatic subjects with FTLD-CDR-SOB-NM scores greater than 0, less than 4 versus PPD, 4) Noncarrier controls versus PPD.

As a follow-up, Receiver Operating Characteristic (ROC) curve analyses were performed using our raw blood-based NfL values to establish the best global blood-based NfL cutoff for distinguishing symptomatic genetic FTD from PPD, late presymptomatic genetic carriers from PPD, mildly symptomatic genetic FTD carriers from PPD, and controls from PPD. The optical cutoff was estimated with the Youden's index (J = sensitivity + specificity −1) when $J > 0.5$ and with the area under the curve (AUC). We also tested the precision of previously established clinical blood-based NfL cutoff of 17.0 pg/mL for all ages (40+) in differentiating symptomatic FTD from PPD was evaluated based on its accuracy, sensitivity, and specificity.[14] According to the previously established cutoff, raw blood-based NfL values were used to determine the percentage of true positives and false negatives to accurately classify symptomatic FTD versus PPD.

Results

Demographic and clinical characteristics

The demographic and clinical characteristics as well as the blood-based NfL values of the selected participants of the study are seen in Table 1. Unless stated otherwise, we reported results as mean ± standard deviation (SD).

As shown in Table 2, the blood-based NfL levels of all patients (FTD and PPD combined) showed a positive moderate correlation with age ($r = 0.346$, $p < 0.001$). Furthermore, the analysis revealed no differences in NfL levels all male and female participants of this study (FTD and PPD combined), $F (1305) = 0.005$ ($p = 0.946$).

Blood-based log NfL in symptomatic genetic FTD carriers compared to PPD

The analysis revealed a significant main effect of the group on blood-based log NfL levels, $F (3, 997) = 156.12$

($p < 0.001$, $\eta_p^2 = 0.320$). Simple contrasts revealed higher blood-based log NfL levels adjusted for age and sex in *C9orf72* (*EMM* = 1.48, *SE* = 0.03, $p < 0.001$, *d* = 1.59, mean NfL = 51.8 pg/mL), *MAPT* (*EMM* = 1.34, *SE* = 0.04, $p < 0.001$, *d* = 1.05, mean NfL = 28.9 pg/mL) and *GRN* mutation carriers (*EMM* = 1.74, *SE* = 0.03, $p < 0.001$, *d* = 2.32, mean NfL = 90.1 pg/mL), compared to individuals with PPD (*EMM* = 1.09, *SE* = 0.01, mean NfL = 14.1 pg/mL). The sex by group interaction was not statistically significant, $F(3, 997) = 2.26$, $p = 0.08$, $\eta_p^2 = 0.007$. Figure 1 shows the log transformed values in blood-based NfL across the three groups.

Blood-based log NfL in late presymptomatic genetic FTD carriers compared to PPD

The analysis found an overall significant main effect of group on adjusted blood-based log NfL means, $F (3, 950) = 3.01$ ($p = 0.029$, $\eta_p^2 = 0.009$). Simple contrasts revealed that the main effect was due to differences in the late presymptomatic *GRN* group, which had slightly lower blood-based NfL levels adjusted for covariates (*EMM* = 1.00, *SE* = 0.03, $p = 0.013$, *d* = 0.36, mean NfL = 14.4 pg/mL) than PPD (*EMM* = 1.08, *SE* = 0.01, mean NfL = 14.1 pg/mL), but with a small effect size. No significant differences were found between the other late presymptomatic mutation carriers, *C9orf72* (*EMM* = 1.13, *SE* = 0.04, $p = 0.165$, *d* = 0.25, mean NfL = 22.3 pg/mL) and *MAPT* (*EMM* = 1.12, *SE* = 0.06, $p = 0.476$, *d* = 0.18, mean NfL = 14.5 pg/mL) compared to PPD. The sex by group interaction was not statistically significant, $F(3, 950) = 2.35$, $p = 0.07$, $\eta_p^2 = 0.007$. Figure 2 shows the log transformed values in blood-based NfL across the three groups.

Blood-based log NfL in mildly symptomatic genetic mutation carriers with 0 < FTLD-CDR-SOB-NM < 4 compared to PPD

In a GLM with age and sex as covariates, we found a significant difference in blood-based log NfL levels between groups, $F(3, 855) = 23.57$ ($p < 0.001$, $\eta_p^2 = 0.076$). Simple contrasts showed elevated blood-based log NfL adjusted for covariates in *C9orf72* (*EMM* = 1.36, *SE* = 0.07, $p < 0.001$, *d* = 1.36, mean NfL = 35.6 pg/mL) and *GRN* (*EMM* = 1.86, *SE* = 0.11, $p < 0.001$, *d* = 3.80, mean NfL = 80.4 pg/mL) compared to patients with PPD (*EMM* = 1.07, *SE* = 0.01, mean NfL = 14.1 pg/mL). No significant differences were found between blood-based log NfL levels adjusted for covariates in *MAPT* (*EMM* = 1.13, *SE* = 0.15, $p = 0.691$, *d* = 0.28, mean NfL = 18.9 pg/mL) carriers but there were only two subjects in this group. The sex by group interaction was not statistically significant,

**Table 1.** Descriptive statistics of GENFI and BbS cohort.

| | GENFI | | | | | | | | | | BbS |
| | Symptomatic* | | | Late presymptomatic | | | Mildly symptomatic† | | | Noncarriers | |
Variable	C9orf72	GRN	MAPT	C9orf72	GRN	MAPT	C9orf72	GRN	MAPT		PPD
N [% female]	73 [34.2]	55 [47.3]	30 [40.0]	38 [73.7]	55 [56.4]	18 [72.2]	9 [55.6]	4 [50.0]	2 [100.0]	190 [57.4]	848 [42.8]
NfL (pg/mL)	51.8 (±45.3)	90.1 (±51.8)	28.9 (±16.1)	22.3 (±30.8)	14.4 (±12.9)	14.5 (±9.0)	35.6 (±21.2)	80.4 (±33.8)	18.9 (±1.5)	11.9 (±9.9)	14.1 (±9.7)
Age at NfL (y)	64.3 (±8.0)	64.0 (±7.8)	59.6 (±7.6)	54.9 (±8.1)	58.6 (±7.2)	52.6 (±9.0)	60.3 (±6.0)	53.5 (±2.2)	62.8 (±4.5)	54.7 (±10.3)	52.8 (±8.3)
Education (y)	13.6 (±3.7)	11.6 (±3.8)	12.8 (±3.7)	14.2 (±3.1)	14.0 (±3.4)	14.4 (±2.7)	13.7 (±5.2)	13.0 (±2.2)	17.0 (±0.0)	14.1 (±3.7)	–
Diagnosis [%]											
AD	–	1.8	–	–	–	–	–	–	–	–	–
ALS	12.3	–	–	–	–	–	8.9	–	–	–	–
Bipolar	–	1.8	–	–	–	–	–	–	–	–	–
bvFTD	67.1	43.6	93.3	–	–	–	6.7	3.8	10.5	–	–
CBS	–	1.8	–	–	–	–	–	–	–	–	–
Dementia	2.7	1.8	3.3	–	–	–	2.2	–	–	–	–
FTD-ALS	11.0	–	–	–	–	–	–	–	–	–	–
Other	2.7	–	–	–	–	–	–	–	–	–	–
PD	–	1.8	–	–	–	–	–	–	–	–	–
PPA	2.7	47.3	3.3	–	–	–	2.2	3.8	–	–	–
PSP	–	1.8	–	–	–	–	–	–	–	–	–
None	1.4	–	–	–	–	–	80.0	92.3	89.5	–	–

Values are reported as mean ± SD, unless stated. NfL: neurofilament light. Subject age was expressed in years according to the age at the last NfL measurement visit, education was measured as the total amount in years at the time of the last NfL measurement. NfL values are the unadjusted plasma NfL for the GENFI cohort and serum NfL for BBS cohort. *Symptomatic group includes 15 patients from mildly symptomatic. †Mildly symptomatic genetic FTD mutation carriers with $0 <$ FTLD-CDR-SOB-NM scores < 4.

Table 2. GLM univariate analyses of variance in NfL levels of symptomatic, late presymptomatic, mildly symptomatic genetic FTD carriers and noncarrier controls compared to PPD.

Source	Sum of Squares	df	MS	F	p	η_p^2
Age						
Symptomatic FTD vs. PPD	11.00	1	11.00	204.51	<0.001	0.170
Late presymptomatic FTD vs. PPD	14.37	1	14.37	316.88	<0.001	0.250
Mildly symptomatic FTD vs. PPD	12.39	1	12.39	274.64	<0.001	0.243
Noncarrier control vs. PPD	14.75	1	14.75	333.47	<0.001	0.244
Sex						
Symptomatic FTD vs. PPD	0.00	1	0.00	0.00	0.991	0.000
Late presymptomatic FTD vs. PPD	0.03	1	0.03	0.60	0.439	0.001
Mildly symptomatic FTD vs. PPD	0.02	1	0.02	0.06	0.362	0.000
Noncarrier control vs. PPD	0.16	1	0.16	3.54	0.060	0.003
Group						
Symptomatic FTD vs. PPD	25.21	3	8.40	156.12	<0.001	0.320
Late presymptomatic FTD vs. PPD	0.41	3	0.14	3.01	0.029	0.009
Mildly symptomatic FTD vs. PPD	3.19	3	1.06	23.57	<0.001	0.076
Noncarrier control vs. PPD	1.36	1	1.36	30.75	<0.001	0.029
Error						
Symptomatic FTD vs. PPD	53.66	997	0.05	–	–	–
Late presymptomatic FTD vs. PPD	43.09	950	0.04	–	–	–
Mildly symptomatic FTD vs. PPD	38.58	855	0.04	–	–	–
Noncarrier control vs. PPD	45.74	1034	0.04	–	–	–

Mildly symptomatic genetic FTD carriers were classified as the symptomatic carriers with 0 < FTLD-CDR-SOB-NM scores < 4. Significance set at $\alpha = 0.05$.
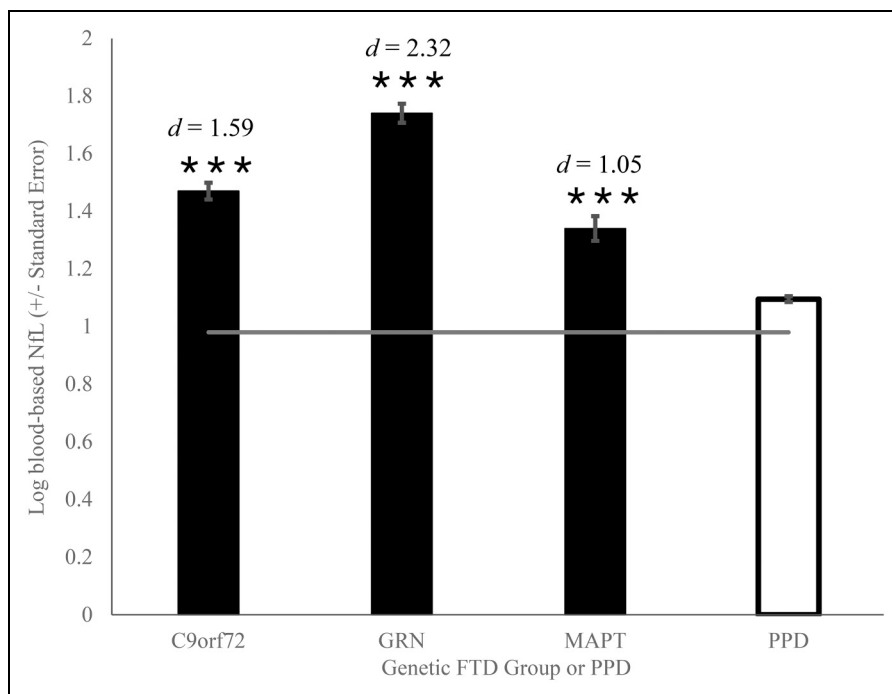
Figure 1. Blood-based Log NfL levels in symptomatic genetic FTD carriers and PPD. Mean plasma log NfL in symptomatic GENFI *C9orf72, GRN,* and *MAPT* mutation carriers compared to mean serum log NfL in BbS PPD patients. Horizontal line represents the benchmark mean plasma log NfL in GENFI noncarrier controls. ***$p < 0.001$ compared to BbS PPD patients.
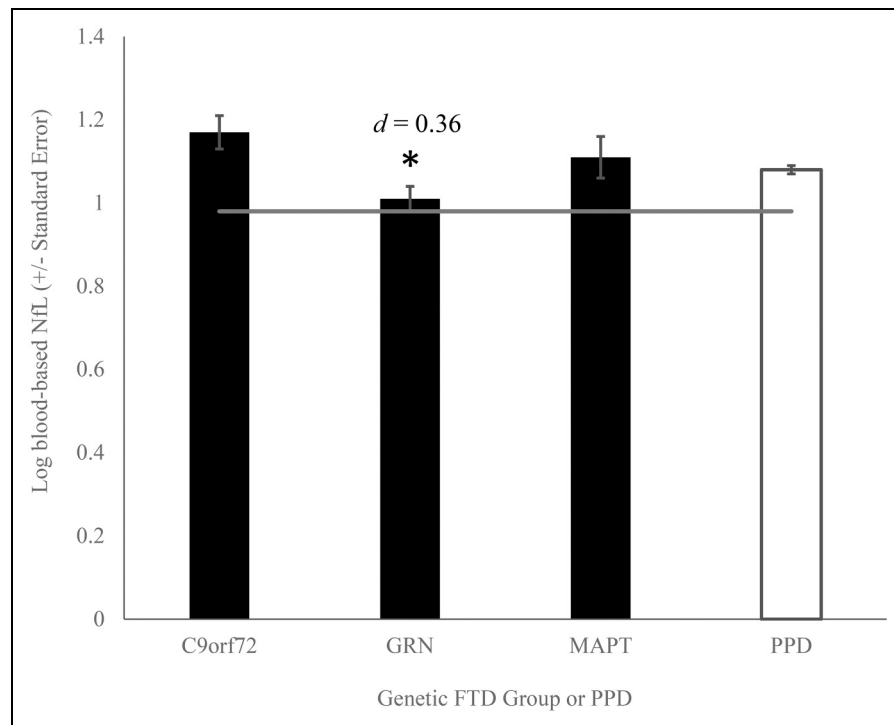
Figure 2. Blood-based Log NfL levels in late presymptomatic genetic FTD carriers and PPD. Mean plasma log NfL in late presymptomatic GENFI *C9orf72*, *GRN*, and *MAPT* mutation carriers compared to mean serum log NfL in BbS PPD patients. Horizontal line represents the benchmark mean plasma log NfL in GENFI noncarrier controls. *$p < 0.05$ compared to BbS PPD patients.

$F(2, 855) = 1.16$, $p = 0.31$, $\eta_p^2 = 0.003$. Figure 3 shows the log transformed values in blood-based NfL across the three groups.

Blood-based log NfL in noncarrier controls compared to PPD

As shown in Figure 4, we detected lower blood-based log NfL levels adjusted for covariates in the noncarrier controls (*EMM* $= 0.98$, *SE* $= 0.02$, $d = 0.48$, mean NfL $= 11.9$ pg/mL) compared to patients with PPD (*EMM* $= 1.08$, *SE* $= 0.01$, mean NfL $= 14.1$ pg/mL), F $(1, 1033) = 33.68$ ($p < 0.001$, $\eta_p^2 = 0.032$). The sex by group interaction was statistically significant, $F(1, 1033) = 7.54$, $p = 0.006$, $\eta_p^2 = 0.007$, and showed that male and female PPD had higher blood-based NfL than male and female GENFI controls, respectively. Moreover, whereas within the PPD group men had higher blood-based NfL than females as previously reported,[14] this sex difference was not detected in the GENFI controls ($p = 0.095$).

Sensitivity analysis factoring the 1-plex GENFI concentration with 1.25

The main analyses using the corrected GENFI plasma NfL (correcting the values to 1.25 the original) concentrations,

and including sex and age as covariates, yielded similar results with those of the uncorrected data. A GLM comparing late presymptomatic GENFI carriers to PPD showed the same overall result as with the uncorrected data with a significant difference in blood-based log NfL between the two groups (Supplemental Table 1). However, when the late presymptomatic carriers were divided by genetic subtype, simple contrasts revealed that the observed difference was due to higher blood-based NfL levels in *C9orf72* compared to PPD (Supplemental Table 1). This result differs from the uncorrected analysis, in which the difference was due to lower blood-based log NfL in the *GRN* carriers compared to PPD. Furthermore, the GLM comparing noncarrrier GENFI controls to PPD showed no significant difference in blood-based log NfL between groups (Supplemental Table 1), which contrasts with the results observed using the uncorrected data.

Accuracy of blood-based NfL cutoffs to distinguish symptomatic, late pre-symptomatic, mildly symptomatic, and non-carriers from PPD

ROC curve analyses with our data revealed that a blood-based NfL cutoff of 22.1 pg/mL, $J = 0.647$ discriminated symptomatic genetic FTD from PPD with 78.5%
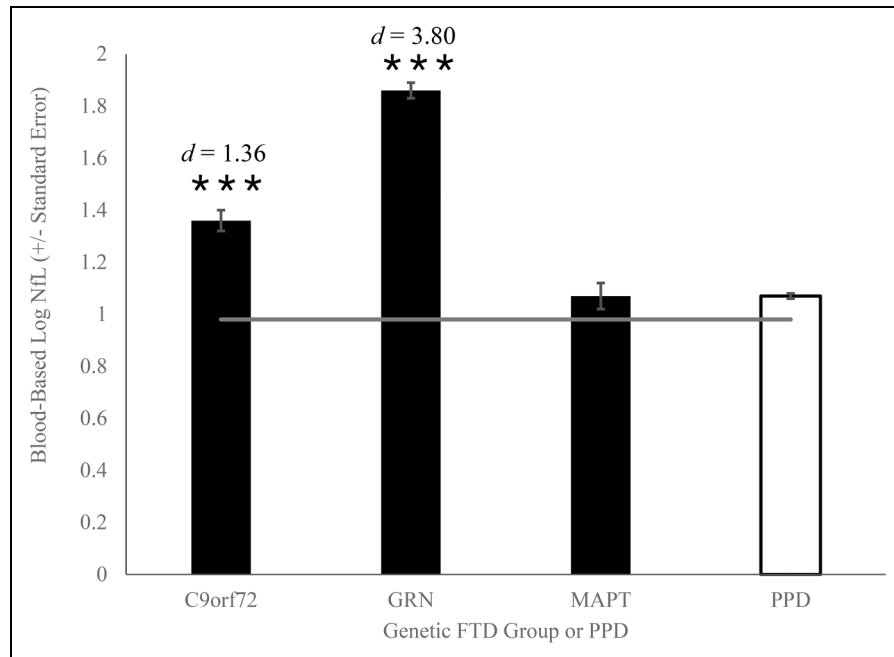
Figure 3. Blood-based Log NfL levels in mildly symptomatic (0 < FTLD-CDR-SOB-NM < 4) Genetic FTD Carriers and PPD. Mean plasma log NfL in mildly symptomatic GENFI genetic mutation carriers with 0 < FTLD-CDR-SOB-NM < 4 versus mean serum log NfL in BbS PPD patients. Horizontal line represents the benchmark mean plasma log NfL in GENFI noncarrier controls. ***$p < 0.001$ compared to BbS PPD patients.
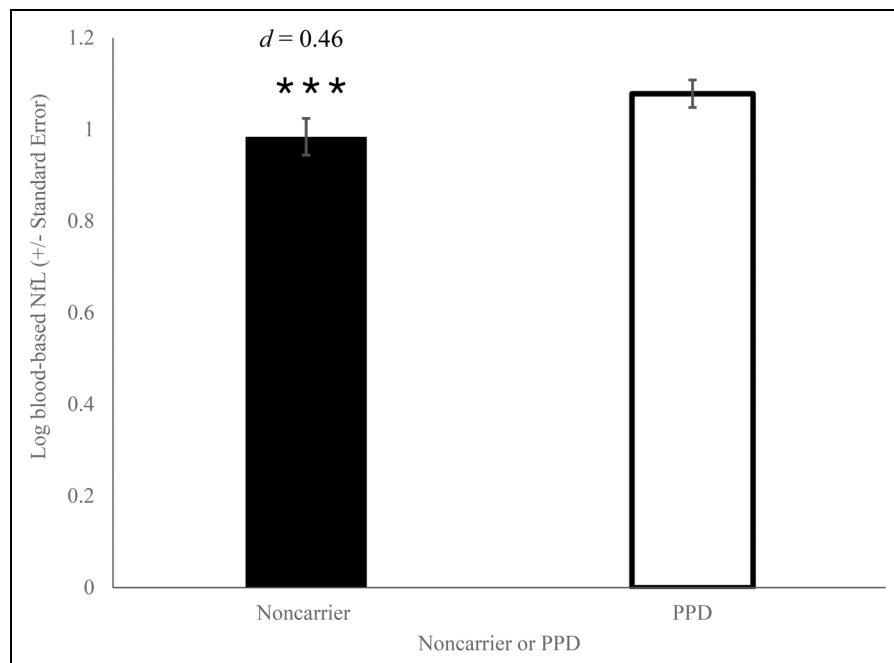

Figure 4. Blood-Based Log NfL levels in noncarrier controls and PPD. Mean plasma log NfL in noncarrier controls versus mean serum log NfL in BbS PPD patients. ***$p < 0.001$ compared to PPD.

sensitivity, 86.2% specificity, and AUC = 0.908. The ROC curve analysis did not find an efficient cutoff to differentiate the late presymptomatic genetic FTD from group from PPD (NfL cutoff of 8.08 pg/mL, $J = 0.113$, 85.6% sensitivity, 25.7% specificity, and AUC = 0.539).When discriminating mildly symptomatic genetic FTD from PPD, the ROC curve analysis revealed that a blood-based NfL cutoff of 16.2 pg/mL, $J = 0.601$ could differentiate the groups with

86.7% sensitivity and 73.5% specificity with an AUC of 0.870. As expected, ROC analysis revealed that NfL is not a good test to differentiate non-carrier controls from PPD (at a cutoff of 64.0 pg/mL, $J = 0.006$, 1.1% sensitivity, and 99.5% specificity with an AUC of 0.410).

ROC curves analyses on serum samples from the PPD cohort previously determined a global blood-based NfL cutoff of 17.0 pg/mL in distinguishing patients with sporadic bvFTD from PPD with 82.9% sensitivity, 76.1% specificity, and AUC = 0.847.[14] Using this cutoff in the current GENFI sample, symptomatic genetic FTD could be discriminated from PPD with 77.8% accuracy, 87.3% sensitivity and 76.1% specificity. It further discriminated mildly symptomatic genetic FTD carriers (0 < FTLD-CDR_SOB-NM < 4) from PPD patients with 76.1% accuracy, 80.0% sensitivity, and 76.1% specificity.

Discussion

This study aimed to test whether blood-based NfL levels differed between genetic frontotemporal dementia mutation carriers (*C9orf72, GRN, MAPT*) and patients with primary psychiatric disorders, at various disease stages, and to determine the accuracy of blood-based NfL as a biomarker to differentiate genetic FTD from PPD using a previously determined cutoff.[14] First, we confirmed that blood-based NfL levels were significantly elevated in all symptomatic genetic FTD mutation carriers compared to patients with PPD. Second, we found that late presymptomatic *GRN* mutation carriers had slightly lower blood-based NfL levels compared to PPD (but not compared to controls), whereas no significant differences were found with the *C9orf72* and *MAPT* carriers. In genetic FTD carriers with mild symptoms, as defined by having FTLD-CDR-SOB-NM scores less than 4, the *C9orf72* mutation carriers showed mildly elevated blood-based NfL, while *GRN* mutation carriers showed even greater elevation in blood-based NfL compared to individuals with PPD. Finally, the noncarrier controls had lower blood-based NfL levels compared to those with PPD, consistent with previous results from Light et al. (2024),[14] which reported slightly higher serum NfL levels in PPD compared to the Banque Signature controls. Furthermore, we demonstrate that both ROC curve based cutoffs showed moderately high discriminatory potential in differentiating the symptomatic GENFI carriers from PPD, with only a slight decrease in accuracy to distinguish PPD from mild cases.

The finding of elevated blood-based NfL levels in symptomatic genetic FTD participants compared to patients with PPD aligns with previous findings in the field.[38–40] Consistent with other studies, *GRN* mutation carriers had the highest levels of NfL.[26,38,39,41] This elevated blood-based NfL could be explained by the fast rate of brain atrophy found in *GRN* carriers as found in previous

studies, reflecting a possibly faster rate of disease progression.[42–44]

In the individuals presenting very mild symptoms, blood-based NfL levels were elevated in *C9orf72* and *GRN* mutation carriers with FTLD-CDR-SOB-NM scores < 4 compared to PPD (no difference in MAPT but there were only two cases). The mildly symptomatic *GRN* had the highest mean blood-based NfL which is expected due to the course of the disease in which blood-based NfL rise sharply near symptom onset.[16,17] The more modest elevated mean log blood-based NfL found in these mildly symptomatic *C9orf72* carriers could be explained by the course of the disease which involves a long late presymptomatic phase in which blood-based NfL levels slowly rises years before onset.[16,17] In the sensitivity analyses, presymptomatic *C9orf72* carriers were also shown to possibly have slightly higher values.

Of note, late presymptomatic *GRN* mutation carriers had significantly lower mean blood-based log-NfL compared to PPD, although the effect was small. This observation is unexpected given that some late presymptomatic rise was previously reported, however this could be due to the rise occurring just prior onset (and therefore not present on average in carriers many over the ten years prior to onset). Alternatively, given that EYO is a modest predictor of actual distance to symptom onset in GRN mutations, it is possible that the slightly lower NfL identified in the late presymptomatic GRN group could have been due to a random sampling effect. However, as seen in the sensitivity analysis, these differences were negligible with the corrected blood-based NfL concentrations. Blood-based NfL values of these late presymptomatic *GRN* mutation carriers might align more closely to controls than to the mildly elevated values seen in PPD for most of the late presymptomatic disease course.[16,17] This pattern is distinct from the course of blood-based NfL in *C9orf72,* in which NfL levels slowly rise early on, leading to significant signals when pooling subject data from many years before onset. It is unclear in *MAPT* given the proposed disease progression of *MAPT*, in which NfL levels only begin to rise after symptom onset, why their late presymptomatic blood-based NfL levels were not lower than PPD (a similar finding to *GRN* in this context; i.e., mildly lower than PPD like controls), but the sample size is small.[16,17]

Our established cutoff of 22.1 pg/mL demonstrated discriminative efficacy in distinguishing symptomatic genetic FTD from PPD, with moderate sensitivity and specificity of 78.5% and 86.2%, respectively. The high AUC value of 0.908 further underscores the robust potential of this cutoff as an optimal cutoff compared to those previously established. Similarly, the cutoff of 16.2 pg/mL established for the mildly symptomatic group was promising with 86.7% sensitivity and 73.5% specificity and AUC of 0.870 that is only slightly lower than in the full symptomatic group. The cutoff in the mildly symptomatic group was

very close to the previously established cutoff from Light et al. (2024)[14] in sporadic FTD. Globally, our results showed similar diagnostic performance compared to the previous study done by Eratne et al. (2024), who used a blood-based NfL cutoff of 13.3pg/mL in patients aged 43–80 years old (AUC 0.91, 86% sensitivity, 78% specificity).

This study has a few limitations. Although a strength of the study is diversity of sites from a number of different countries, the sites are primarily located in Canada and Europe. Other limitations include the relatively small sample sizes of the genetic FTD mutation groups once broken down per mutation and disease stage, limiting our ability to assess a pure mildly symptomatic group, or to test for meaningful sex differences. A strength however is the relatively large sample size for each sex in PPD and GENFI controls. Light et al. (2024)[14] previously reported higher NfL in PPD males compared to females which was replicated in the current analyses but here we extend those data by showing that both males and females with PPD have higher blood-based NfL than the respective GENFI controls, and importantly, a sex difference was not detected in the GENFI controls. This suggests that a biological mechanism related to PPD may be driving the sex difference in blood-based NfL. Thus, this data may provide a basis for future studies aimed at identifying the factors that lead to inconsistent reports in the literature regarding sex differences in blood-based NfL. Although it is unclear what may be driving the higher blood-based NfL in male patients with PPD, we have recently found higher inflammatory markers within PPD patients with high blood-based NfL (unpublished observations), and there are important sex-differences in inflammation, providing one avenue for future research.[45,46] Yet, we cannot entirely rule out the possibility that a small number of the PPD patients could have been at the beginning of a neurodegenerative disease without pathological data. Additionally, we did not have creatinine data in GENFI, but we excluded BBS subjects with clinically significant kidney failure. The diagnoses in the BbS cohort were established clinically using standard psychiatric diagnostic processes. Final psychiatric disorders were observed at discharge, following a period of observation to distinguish transient psychiatric symptoms from more sustained psychiatric disorders. While this approach cannot rule with absolute certainty a psychiatric presentation of an early stage of neurodegenerative disorder, the amount of such cases would be at most marginal. Furthermore, our study involved the use of two different blood sources of NfL. However, previous studies have reported plasma and serum NfL to be comparable and that NfL is a stable measure, being robust across the GENFI cohort.[47] Another limitation is that the blood-based NfL measurements were performed in two different laboratories at different times with different assays. However, it has been found that intra-lab consistency is high.[47] Moreover, it is known that the 4-plex NfL assay (used to analyze the BbS data) generates higher blood-based NfL concentrations than the 1-plex NfL assay (used to analyze the GENFI data). Method comparisons performed in the laboratories that generated the data in the current study have seen strong positive and linear relationships between the two assays (correlations >0.95), but 1.1- to 1.4-fold higher blood-based NfL concentrations by 4-plex compared with the 1-plex (Supplemental Figure 1 from H. Zetterberg). The sensitivity analysis which factored the 1-plex GENFI plasma NfL values by 1.25, showed overall very similar results as with the uncorrected pooled data. We recognize that it would have been ideal to conduct measurements at a single laboratory, with the same assay and from patients in the same location for more accurate results, however due to funding constraints. this was not possible. Further, the heterogeneity of psychiatric disorders in the PPD cohort presents another potential limitation, as previous studies have reported variations in NfL levels across psychiatric conditions.[48] However, a study by Light et al. (2024)[14] which analyzed the same PPD cohort, found no significant differences in NfL levels across psychiatric subgroups. Nonetheless, future studies should continue to explore the sensitivity of NfL for differentiating psychiatric conditions to enhance the biomarker's potential utility. While the study of prodromal/mild genetic FTD provides a window on the use of sNfL in the very early stages, it remains uncertain if findings would generalize to sporadic cases. Prospective studies will be required to determine the value of this biomarker in ambiguous/very early sporadic cases in real-life clinical settings. Further, future analysis comparing the same type of blood-based NfL at a single laboratory with the same assay should be done for more accurate results. Our identified cutoffs however, being very close to the previously published cutoffs reinforce the robustness of the blood-based NfL measurement method.

In conclusion, our study introduces valuable evidence towards the use of blood-based NfL in differentiating patients with symptomatic genetic FTD from a large cohort of PPD patients across various psychiatric disorders, including for patients with very mild FTD symptoms.[9,12] Given the slight increase of serum NfL in PPD, the accuracy of NfL to distinguish PPD from pure psychiatric *C9orf72* prodromes remains to be established. Future research should further determine if rate of change of blood-based NfL levels overtime is a better diagnostic biomarker than cross-sectional measure for this clinical purpose. In addition, combining blood-based NfL with other peripheral biomarkers of neuronal degeneration could be further investigated.

ORCID iDs

Ella Liu ⓘ https://orcid.org/0009-0003-1854-9835

Sherri Lee Jones ⓘ https://orcid.org/0000-0003-0511-7198

Victoria Light ⓘ https://orcid.org/0009-0000-0621-7970

Charlotte Teunissen ⓘ https://orcid.org/0000-0002-4061-0837

Arabella Bouzigues ⓘ https://orcid.org/0000-0002-0267-8590

Lucy L Russell ⓘ https://orcid.org/0000-0001-5023-5893

Phoebe H Foster ⓘ https://orcid.org/0000-0001-6300-6598

Eve Ferry-Bolder ⓘ https://orcid.org/0009-0006-5083-0901

Harro Seelaar ⓘ https://orcid.org/0000-0003-1989-7527

Robert Laforce ⓘ https://orcid.org/0000-0002-2031-490X

Caroline Graff ⓘ https://orcid.org/0000-0002-9949-2951

Daniela Galimberti ⓘ https://orcid.org/0000-0002-9284-5953

Rik Vandenberghe ⓘ https://orcid.org/0000-0001-6237-2502

Alexandre de Mendonça ⓘ https://orcid.org/0000-0002-0488-1453

Isabel Santana ⓘ https://orcid.org/0000-0002-8114-9434

Alexander Gerhard ⓘ https://orcid.org/0000-0002-8071-6062

Johannes Levin ⓘ https://orcid.org/0000-0001-5092-4306

Maria Carmela Tartaglia ⓘ https://orcid.org/0000-0002-5944-8497

Matthis Synofzik ⓘ https://orcid.org/0000-0002-2280-7273

Fermin Moreno ⓘ https://orcid.org/0000-0001-5200-3164

Barbara Borroni ⓘ https://orcid.org/0000-0001-9340-9814

Henrik Zetterberg ⓘ https://orcid.org/0000-0003-3930-4354

Simon Ducharme ⓘ https://orcid.org/0000-0002-7309-1113

Isabelle Le Ber ⓘ https://orcid.org/0000-0002-2508-5181

Ethical considerations

Each research center in the GENFI study received approval from their local ethics committees prior to the start of the review.[18] This project was approved by the McGill University Health Center's Research Ethics Board.

All participants in the Banque Signature study signed an informed consent form and the study received approval from the local scientific evaluation and research ethics committees of the Louis-H. Lafontain Hospital (renamed in March 2013 as CER-CEMTL) following the *Declaration of Helsinki*.[24]

Consent to participate

All participants of the GENFI and Banque Signature studies provided written informed consent per the *Declaration of Helsinki prior to enrolment*.[18]

Author contributions

Ella Liu: Formal analysis; Software; Visualization; Writing – original draft.

Sherri Lee Jones: Resources; Software; Supervision; Validation; Writing – review & editing.

Victoria Light: Writing – review & editing.

Charlotte Teunissen: Data curation; Resources; Writing – review & editing.

Arabella Bouzigues: Data curation; Resources; Writing – review & editing.

Lucy Russell: Data curation; Resources; Writing – review & editing.

Phoebe Foster: Data curation; Resources; Writing – review & editing.

Eve Ferry-Bolder: Data curation; Resources; Writing – review & editing.

John van Swieten: Data curation; Resources; Writing – review & editing.

Lize Jiskoot: Data curation; Resources; Writing – review & editing.

Harro Seelaar: Data curation; Resources; Writing – review & editing.

Raquel Sanchez-Valle: Data curation; Resources; Writing – review & editing.

Robert Laforce: Data curation; Resources; Writing – review & editing.

Caroline Graff: Data curation; Resources; Writing – review & editing.

Daniela Galimberti: Data curation; Resources; Writing – review & editing.

Rik Vandenberghe: Data curation; Resources; Writing – review & editing.

Alexandre de Mendonca: Data curation; Resources; Writing – review & editing.

Pietro Tiraboschi: Data curation; Resources; Writing – review & editing.

Isabel Santana: Data curation; Resources; Writing – review & editing.

Alexandre Gerhard: Data curation; Resources; Writing – review & editing.

Johannes Levin: Data curation; Resources; Writing – review & editing.

Sandro Sorbi: Data curation; Resources; Writing – review & editing.

Markus Otto: Data curation; Resources; Writing – review & editing.

Isabelle Le Ber: Data curation; Resources; Writing – review & editing.

Elizabeth Finger: Data curation; Resources; Writing – review & editing.

Maria Carmela Tartaglia: Data curation; Resources; Writing – review & editing.

Mario Masellis: Data curation; Resources; Writing – review & editing.

James Rowe: Data curation; Funding acquisition; Resources; Writing – review & editing.

Matthis Synofzik: Data curation; Resources; Writing – review & editing.

Fermin Moreno: Data curation; Resources; Writing – review & editing.

Barbara Borroni: Data curation; Resources; Writing – review & editing.

Henrik Zetterberg: Data curation; Resources; Validation; Writing – review & editing.

Jonathan Rohrer: Data curation; Resources; Writing – review & editing.

Simon Ducharme: Conceptualization; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing – review & editing.

Funding

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: SD conducts sponsored clinical trial research (Biogen, NovoNordisk, Innodem Neurosciences, Janssen, Alnylam) and has received advisory/speaker fees (Eisai, QuRALIS, Eli Lilly). JBR provides consultancy unrelated to the current work to Asceneuron, Astronautx, Astex, Curasen, CumulusNeuro, Wave, SVHealth, and has research grants from AZ-Medimmune, Janssen, and Lilly as industry partners in the Dementias Platform UK. The other authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability statement

The data supporting the findings of this study are not publicly available due to privacy or ethical restrictions.

Supplemental material

Supplemental material for this article is available online.

References

1. Rademakers R, Neumann M and Mackenzie IR. Advances in understanding the molecular basis of frontotemporal dementia. *Nat Rev Neurol* 2012; 8: 423–434.

2. Ducharme S, Price BH, Larvie M, et al. Clinical approach to the differential diagnosis between behavioral variant frontotemporal dementia and primary psychiatric disorders. *Am J Psychiatry* 2015; 172: 827–837.

3. Ducharme S, Pijnenburg Y, Rohrer JD, et al. Identifying and diagnosing TDP-43 neurodegenerative diseases in psychiatry. *Am J Geriatr Psychiatry* 2024; 32: 98–113.

4. Levy JP, Bocti C, Elie D, et al. Bifrontal hypermetabolism on brain FDG-PET in a case of C9orf72-related behavioral variant of frontotemporal dementia. *J Neuropsychiatry Clin Neurosci* 2019; 31: 92–94.

5. Petzold A. Neurofilament phosphoforms: surrogate markers for axonal injury, degeneration and loss. *J Neurol Sci* 2005; 233: 183–198.

6. Thebault S, Booth RA and Freedman MS. Blood neurofilament light chain: the neurologist's troponin? *Biomedicines* 2020; 8: 523.

7. Harp C, Thanei GA, Jia X, et al. Development of an age-adjusted model for blood neurofilament light chain. *Ann Clin Transl Neurol* 2022; 9: 444–453.

8. Khalil M, Pirpamer L, Hofer E, et al. Serum neurofilament light levels in normal aging and their association with morphologic brain changes. *Nat Commun* 2020; 11: 812.

9. Al Shweiki MR, Steinacker P, Oeckl P, et al. Neurofilament light chain as a blood biomarker to differentiate psychiatric disorders from behavioural variant frontotemporal dementia. *J Psychiatr Res* 2019; 113: 137–140.

10. Barro C, Chitnis T and Weiner HL. Blood neurofilament light: a critical review of its application to neurologic disease. *Ann Clin Transl Neurol* 2020; 7: 2508–2523.

11. Ducharme S, Dols A, Laforce R, et al. Recommendations to distinguish behavioural variant frontotemporal dementia from psychiatric disorders. *Brain* 2020; 143: 1632–1650.

12. Katisko K, Cajanus A, Jääskeläinen O, et al. Serum neurofilament light chain is a discriminative biomarker between frontotemporal lobar degeneration and primary psychiatric disorders. *J Neurol* 2020; 267: 162–167.

13. Verde F, Otto M and Silani V. Neurofilament light chain as biomarker for amyotrophic lateral sclerosis and frontotemporal dementia. *Front Neurosci* 2021; 15: 679199.

14. Light V, Jones SL, Rahme E, et al. Clinical accuracy of serum neurofilament light to differentiate frontotemporal dementia from primary psychiatric disorders is age-dependent. *Am J Geriatr Psychiatry* 2024; 32: 988–1001.

15. Saracino D, Dorgham K, Camuzat A, et al. Plasma NfL levels and longitudinal change rates in *C9orf72* and *GRN*-associated diseases: from tailored references to clinical applications. *J Neurol Neurosurg Psychiatry* 2021; 92: 1278–1288.

16. Gendron TF, Heckman MG, White LJ, et al. Comprehensive cross-sectional and longitudinal analyses of plasma neurofilament light across FTD spectrum disorders. *Cell Rep Med* 2022; 3: 100607.

17. Staffaroni AM, Quintana M, Wendelberger B, et al. Temporal order of clinical and biomarker changes in familial frontotemporal dementia. *Nat Med* 2022; 28: 2194–2206.

18. Rohrer JD, Nicholas JM, Cash DM, et al. Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis. *Lancet Neurol* 2015; 14: 253–262.

19. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology* 2011; 76: 1006–1014.

20. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* 2011; 134: 2456–2477.

21. Samra K, Macdougall A, Peakman G, et al. Neuropsychiatric symptoms in genetic frontotemporal dementia: developing a new module for Clinical Rating Scales. *J Neurol Neurosurg Psychiatry* 2023; 94: 357–368.

22. Samra K, MacDougall AM, Peakman G, et al. Motor symptoms in genetic frontotemporal dementia: developing a new module for clinical rating scales. *J Neurol* 2023; 270: 1466–1477.

23. Moore KM, Nicholas J, Grossman M, et al. Age at symptom onset and death and disease duration in genetic frontotemporal dementia: an international retrospective cohort study. *Lancet Neurol* 2020; 19: 145–156.

24. Lupien SJ, Sasseville M, François N, et al. The DSM5/RDoC debate on the future of mental health research: implication for studies on human stress and presentation of the signature bank. *Stress* 2017; 20: 95–111.

25. Giguère CÉ and Potvin S. The Drug Abuse Screening Test preserves its excellent psychometric properties in psychiatric patients evaluated in an emergency setting. *Addict Behav* 2017; 64: 165–170.

26. Heller C, Foiani MS, Moore K, et al. Plasma glial fibrillary acidic protein is raised in progranulin-associated frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 2020; 91: 263–270.

27. Kwon HS, Lee H, Kim YS, et al. Comparing neurofilament light chain levels in serum and plasma. *Dement Neurocogn Disord* 2023; 22: 109–111.

28. Qiu X, Lee S, Jackson J, et al. Equivalence of serum and plasma neurofilament light chain levels using highly sensitive automated immunoassay. *Alzheimers Dement* 2020; 16: e045278.

29. Riffenburgh RH. Chapter 11 - Using the reference guide. *Statistics in medicine*. 2nd ed. London: Academic Press Elsevier, 2006.

30. Mattsson N, Andreasson U, Zetterberg H, et al. Association of plasma neurofilament light with neurodegeneration in patients with Alzheimer disease. *JAMA Neurol* 2017; 74: 557–566.

31. Sánchez-Valle R, Heslegrave A, Foiani MS, et al. Serum neurofilament light levels correlate with severity measures and neurodegeneration markers in autosomal dominant Alzheimer's disease. *Alzheimer Res Ther* 2018; 10: 113.

32. Disanto G, Barro C, Benkert P, et al. Serum Neurofilament light: a biomarker of neuronal damage in multiple sclerosis. *Ann Neurol* 2017; 81: 857–870.

33. Onyike CU and Diehl-Schmid J. The epidemiology of frontotemporal dementia. *Int Rev Psychiatry* 2013; 25: 130–137.

34. Pengo M, Alberici A, Libri I, et al. Sex influences clinical phenotype in frontotemporal dementia. *Neurol Sci* 2022; 43: 5281–5287.

35. Roberson ED, Hesse JH, Rose KD, et al. Frontotemporal dementia progresses to death faster than Alzheimer disease. *Neurology* 2005; 65: 719–725.

36. Pratt J, De Vito G, Segurado R, et al. Plasma neurofilament light levels associate with muscle mass and strength in middle-aged and older adults. Findings from GenoFit. *J Cachexia Sarcopenia Muscle* 2022; 13: 1811–1820.

37. Heidari S, Babor TF, De Castro P, et al. Sex and gender equity in research: rationale for the SAGER guidelines and recommended use. *Res Integr Peer Rev* 2016; 1: 2.

38. Meeter LH, Dopper EG, Jiskoot LC, et al. Neurofilament light chain: a biomarker for genetic frontotemporal dementia. *Ann Clin Transl Neurol* 2016; 3: 623–636.

39. van der Ende EL, Meeter LH, Poos JM, et al. Serum neurofilament light chain in genetic frontotemporal dementia: a longitudinal, multicentre cohort study. *Lancet Neurol* 2019; 18: 1103–1111.

40. Wilke C, Reich S, van Swieten JC, et al. Stratifying the presymptomatic phase of genetic frontotemporal dementia by serum NfL and pNfH: a longitudinal multicentre study. *Ann Neurol* 2022; 91: 33–47.

41. Rojas JC, Wang P, Staffaroni AM, et al. Plasma neurofilament light for prediction of disease progression in familial frontotemporal lobar degeneration. *Neurology* 2021; 96: e2296–e2312.

42. Rohrer JD, Ridgway GR, Modat M, et al. Distinct profiles of brain atrophy in frontotemporal lobar degeneration caused by progranulin and tau mutations. *Neuroimage* 2010; 53: 1070–1076.

43. Whitwell JL, Boeve BF, Weigand SD, et al. Brain atrophy over time in genetic and sporadic frontotemporal dementia: a study of 198 serial magnetic resonance images. *Eur J Neurol* 2015; 22: 745–752.

44. Whitwell JL, Weigand SD, Gunter JL, et al. Trajectories of brain and hippocampal atrophy in FTD with mutations in MAPT or GRN. *Neurology* 2011; 77: 393–398.

45. Klein SL and Flanagan KL. Sex differences in immune responses. *Nat Rev Immunol* 2016; 16: 626–638.

46. Cai H, Zhao T, Pang Y, et al. Systemic inflammatory markers in ageing, Alzheimer's disease and other dementias. *Brain* 2025; 148: 480–492.

47. Linnemann C, Wilke C, Mengel D, et al. Nfl reliability across laboratories, stage-dependent diagnostic performance and matrix comparability in genetic FTD: a large GENFI study. *J Neurol Neurosurg Psychiatry* 2024; 95: 822–828.

48. Bavato F, Barro C, Schnider LK, et al. Introducing neurofilament light chain measure in psychiatry: current evidence, opportunities, and pitfalls. *Mol Psychiatry* 2024; 29: 2543–2559.

Appendix

Collaborators

Genetic Frontotemporal Dementia Initiative (GENFI): Annabel Nelson Department of Neurodegenerative Disease, Dementia Research Centre, UCL Queen Square Institute of Neurology, London, UK; Martina Bocchetta Department of Neurodegenerative Disease, Dementia Research Centre, UCL Queen Square Institute of

Neurology, London, UK; David Cash Department of Neurodegenerative Disease, Dementia Research Centre, UCL Queen Square Institute of Neurology, London, UK; David L Thomas Neuroimaging Analysis Centre, Department of Brain Repair and Rehabilitation, UCL Institute of Neurology, Queen Square, London, UK; Emily Todd Department of Neurodegenerative Disease, Dementia Research Centre, UCL Queen Square Institute of Neurology, London, UK; Hanya Benotmane UK Dementia Research Institute at University College London, UCL Queen Square Institute of Neurology, London, UK; Jennifer Nicholas Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK; Kiran Samra Department of Neurodegenerative Disease, Dementia Research Centre, UCL Queen Square Institute of Neurology, London, UK; Rachelle Shafei Department of Neurodegenerative Disease, Dementia Research Centre, UCL Queen Square Institute of Neurology, London, UK; Carolyn Timberlake Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK; Thomas Cope Department of Clinical Neuroscience, University of Cambridge, Cambridge, UK; Timothy Rittman Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK; Antonella Alberici Centre for Neurodegenerative Disorders, University of Brescia, Brescia, Italy; Enrico Premi Stroke Unit, ASST Brescia Hospital, Brescia, Italy; Roberto Gasparotti Neuroradiology Unit, University of Brescia, Brescia, Italy; Valentina Cantoni Centre for Neurodegenerative Disorders, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy; Emanuele Buratti ICGEB, Trieste, Italy; Andrea Arighi Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurodegenerative Diseases Unit, Milan, Italy; University of Milan, Centro Dino Ferrari, Milan, Italy; Chiara Fenoglio Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurodegenerative Diseases Unit, Milan, Italy; University of Milan, Centro Dino Ferrari, Milan, Italy; Elio Scarpini Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurodegenerative Diseases Unit, Milan, Italy; University of Milan, Centro Dino Ferrari, Milan, Italy; Giorgio Fumagalli Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurodegenerative Diseases Unit, Milan, Italy; University of Milan, Centro Dino Ferrari, Milan, Italy; Vittoria Borracci Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurodegenerative Diseases Unit, Milan, Italy; University of Milan, Centro Dino Ferrari, Milan, Italy; Giacomina Rossi Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy; Giorgio Giaccone Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy; Giuseppe Di Fede Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy; Paola Caroppo Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy; Pietro Tiraboschi Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy; Sara Prioni Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy; Veronica Redaelli Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy; David Tang-Wai The University Health Network, Krembil Research Institute, Toronto, Canada; Ekaterina Rogaeva Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Canada; Miguel Castelo-Branco Faculty of Medicine, University of Coimbra, Coimbra, Portugal; Morris Freedman Baycrest Health Sciences, Rotman Research Institute, University of Toronto, Toronto, Canada; Ron Keren The University Health Network, Toronto Rehabilitation Institute, Toronto, Canada; Sandra Black Sunnybrook Health Sciences Centre, Sunnybrook Research Institute, University of Toronto, Toronto, Canada; Sara Mitchell Sunnybrook Health Sciences Centre, Sunnybrook Research Institute, University of Toronto, Toronto, Canada; Christen Shoesmith Department of Clinical Neurological Sciences, University of Western Ontario, London, Ontario, Canada; Robart Bartha Department of Medical Biophysics, The University of Western Ontario, London, Ontario, Canada; Centre for Functional and Metabolic Mapping, Robarts Research Institute, The University of Western Ontario, London, Ontario, Canada; Rosa Rademakers Center for Molecular Neurology, University of Antwerp Jackie Poos Department of Neurology, Erasmus Medical Center, Rotterdam, Netherlands; Janne M. Papma Department of Neurology, Erasmus Medical Center, Rotterdam, Netherlands; Lucia Giannini Department of Neurology, Erasmus Medical Center, Rotterdam, Netherlands; Rick van Minkelen Department of Clinical Genetics, Erasmus Medical Center, Rotterdam, Netherlands; Yolande Pijnenburg Amsterdam University Medical Centre, Amsterdam VUmc, Amsterdam, Netherlands; Benedetta Nacmias Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy; Camilla Ferrari Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy; Cristina Polito Department of Biomedical, Experimental and Clinical Sciences "Mario Serio", Nuclear Medicine Unit, University of Florence, Florence, Italy; Gemma Lombardi Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy; Valentina Bessi Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy; Michele Veldsman Nuffield Department of Clinical Neurosciences, Medical Sciences Division, University of Oxford, Oxford, UK; Christin Andersson Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; Hakan Thonberg Center for Alzheimer Research, Division of Neurogeriatrics, Karolinska Institutet, Stockholm,

Sweden; Linn Öijerstedt Center for Alzheimer Research, Division of Neurogeriatrics, Department of Neurobiology, Care Sciences and Society, Bioclinicum, Karolinska Institutet, Solna, Sweden; Unit for Hereditary Dementias, Theme Aging, Karolinska University Hospital, Solna, Sweden; Vesna Jelic Division of Clinical Geriatrics, Karolinska Institutet, Stockholm, Sweden; Paul Thompson Division of Neuroscience and Experimental Psychology, Wolfson Molecular Imaging Centre, University of Manchester, Manchester, UK; Tobias Langheinrich Division of Neuroscience and Experimental Psychology, Wolfson Molecular Imaging Centre, University of Manchester, Manchester, UK; Manchester Centre for Clinical Neurosciences, Department of Neurology, Salford Royal NHS Foundation Trust, Manchester, UK; Albert Lladó Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic, Barcelona, Spain; Anna Antonell Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic, Barcelona, Spain; Jaume Olives Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic, Barcelona, Spain; Mircea Balasa Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic, Barcelona, Spain; Nuria Bargalló Imaging Diagnostic Center, Hospital Clínic, Barcelona, Spain; Sergi Borrego-Ecija Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic, Barcelona, Spain; Ana Verdelho Department of Neurosciences and Mental Health, Centro Hospitalar Lisboa Norte - Hospital de Santa Maria Neuroscience Area, Biodonostia Health Research Insitute, San Sebastian, Gipuzkoa, Spain; Ana Gorostidi Neuroscience Area, Biodonostia Health Research Insitute, San Sebastian, Gipuzkoa, Spain; Jorge Villanua OSATEK, University of Donostia, San Sebastian, Gipuzkoa, Spain; Marta Cañada CITA Alzheimer, San Sebastian, Gipuzkoa, Spain; Mikel Tainta Neuroscience Area, Biodonostia Health Research Insitute, San Sebastian, Gipuzkoa, Spain; Miren Zulaica Neuroscience Area, Biodonostia Health Research Insitute, San Sebastian, Gipuzkoa, Spain; Myriam Barandiaran Cognitive Disorders Unit, Department of Neurology, Donostia University Hospital, San Sebastian, Gipuzkoa, Spain; Neuroscience Area, Biodonostia Health Research Insitute, San Sebastian, Gipuzkoa, Spain; Patricia Alves Neuroscience Area, Biodonostia Health Research Insitute, San Sebastian, Gipuzkoa, Spain; Department of Educational Psychology and Psychobiology, Faculty of Education, International University of La Rioja, Logroño, Spain; Benjamin Bender Department of Diagnostic and Interventional Neuroradiology, University of Tübingen, Tübingen, Germany; Lisa Graf Department of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research and Center of Neurology, University of Tübingen, Tübingen, Germany; Annick Vogels Department of Human Genetics, KU Leuven, Leuven, Belgium; Mathieu Vandenbulcke Geriatric Psychiatry Service, University Hospitals Leuven, Belgium; Neuropsychiatry, Department of Neurosciences, KU Leuven, Leuven, Belgium; Philip Van Damme Neurology Service, University Hospitals Leuven, Belgium; Laboratory for Neurobiology, VIB-KU Leuven Centre for Brain Research, Leuven, Belgium; Rose Bruffaerts Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium; Biomedical Research Institute, Hasselt University, 3500 Hasselt, Belgium; Koen Poesen Laboratory for Molecular Neurobiomarker Research, KU Leuven, Leuven, Belgium; Pedro Rosa-Neto Translational Neuroimaging Laboratory, McGill Centre for Studies in Aging, McGill University, Montreal, Québec, Canada; Serge Gauthier Alzheimer Disease Research Unit, McGill Centre for Studies in Aging, Department of Neurology Reference Network for Rare Neurological Diseases (ERN-RND)Anne Bertrand Sorbonne Université, Paris Brain Institute – Institut du Cerveau – ICM, Inserm U1127, CNRS UMR 7225, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France; Inria, Aramis project-team, F-75013, Paris, France; Centre pour l'Acquisition et le Traitement des Images, Institut du Cerveau et la Moelle, Paris, France; Aurélie Funkiewiez Centre de référence des démences rares ou précoces, IM2A, Département de Neurologie, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France; Sorbonne Université, Paris Brain Institute – Institut du Cerveau – ICM, Inserm U1127, CNRS UMR 7225, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France; Daisy Rinaldi Centre de référence des démences rares ou précoces, IM2A, Département de Neurologie, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France; Sorbonne Université, Paris Brain Institute – Institut du Cerveau – ICM, Inserm U1127, CNRS UMR 7225, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France; Département de Neurologie, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France; Dario Saracino Sorbonne Université, Paris Brain Institute – Institut du Cerveau – ICM, Inserm U1127, CNRS UMR 7225, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France; Inria, Aramis project-team, F-75013, Paris, France; Centre de référence des démences rares ou précoces, IM2A, Département de Neurologie, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France; Olivier Colliot Sorbonne Université, Paris Brain Institute – Institut du Cerveau – ICM, Inserm U1127, CNRS UMR 7225, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France; Inria, Aramis project team, F-75013, Paris, France; Centre pour l'Acquisition et le Traitement des Images, Institut du Cerveau et la Moelle, Paris, France; Sabrina Sayah Sorbonne Université, Paris Brain Institute – Institut du Cerveau – ICM, Inserm U1127, CNRS UMR 7225, AP-HP - Hôpital Pitié-Salpêtrière, Paris, France; Catharina Prix Neurologische Klinik,

Ludwig-Maximilians-Universität München, Munich, Germany; Elisabeth Wlasich Neurologische Klinik, Ludwig-Maximilians-Universität München, Munich, Germany; Olivia Wagemann Neurologische Klinik, Ludwig-Maximilians-Universität München, Munich, Germany; Sandra Loosli Neurologische Klinik, Ludwig-Maximilians Universität München, Munich, Germany; Sonja Schönecker Neurologische Klinik, Ludwig-Maximilians-Universität München, Munich, Germany; Tobias Hoegen Neurologische Klinik, Ludwig-Maximilians-Universität München, Munich, Germany; Jolina Lombardi Department of Neurology, University of Ulm, Ulm; Sarah Anderl-Straub Department of Neurology, University of Ulm, Ulm, Germany; Adeline Rollin CHU, CNR-MAJ, Labex Distalz, LiCEND Lille, France; Gregory Kuchcinski Univ Lille, France; Inserm 1172, Lille, France; CHU, CNR-MAJ, Labex Distalz, LiCEND Lille, France; Maxime Bertoux Inserm 1172, Lille, France; CHU, CNR-MAJ, Labex Distalz, LiCEND Lille, France; Thibaud Lebouvier Univ Lille, France; Inserm 1172, Lille, France; CHU, CNR-MAJ, Labex Distalz, LiCEND Lille, France; Vincent Deramecourt Univ Lille, France; Inserm 1172, Lille, France; CHU, CNR-MAJ, Labex Distalz, LiCEND Lille, France; Beatriz Santiago Neurology Department, Centro Hospitalar e Universitario de Coimbra, Coimbra, Portugal; Diana Duro Faculty of Medicine, University of Coimbra, Coimbra, Portugal; Maria João Leitão Centre of Neurosciences and Cell Biology, Universidade de Coimbra, Coimbra, Portugal; Maria Rosario Almeida Faculty of Medicine, University of Coimbra, Coimbra, Portugal; Miguel Tábuas-Pereira Neurology Department, Centro Hospitalar e Universitario de Coimbra, Coimbra, Portugal; Sónia Afonso Instituto Ciencias Nucleares Aplicadas a Saude, Universidade de Coimbra, Coimbra, Portugal

Banque Signature (BbS): Félix-Antoine Bérubé Department of Psychiatry and Addictology, Université de Montréal, Montréal, Québec, Canada; Janick Boissonneault Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada, Canada; Catherine Briand Département d'ergothérapie, Université du Québec à Trois-Rivières, Trois-Rivières; Québec, Canada; Lionel Cailhol Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Department of Psychiatry and Addictology, Université de Montréal, Montréal, Québec, Canada; Enzo Cipriani Department of Psychiatry, Université de Montréal, Montréal, Québec, Canada; Pierre David Faculté de pharmacie, Université de Montréal, Montréal, Québec, Canada; Simon Ducharme Douglas Mental Health University Institute, Department of Psychiatry, McGill University, Montreal, Québec, Canada; Alexandre Dumais Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Department of Psychiatry and Addictology, Université de Montréal, Montréal, Québec, Canada; Helen Findlay Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Montréal, Canada; Steve Geoffrion Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; School of Psychoeducation, Université de Montréal, Montréal, Québec, Canada; Charles-Édouard Giguère Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Stéphane Guay Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Department of Psychiatry and Addictology, Université de Montréal, Montréal, Québec, Canada; Alexandre Hudon Department of Psychiatry and Addictology, Université de Montréal, Montréal, Québec, Canada; Robert-Paul Juster Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Department of Psychiatry and Addictology, Université de Montréal, Montréal, Québec, Canada; Réal Labelle Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Département de Psychologie, Université du Québec à Montréal, Montréal, Québec, Canada; Marc Lavoie Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Department of Psychiatry and Addictology, Université de Montréal, Montréal, Québec, Canada; Myriam Lemire Department of Psychiatry and Addictology, Université de Montréal, Montréal, Québec, Canada; Pierre Léouffre Centre intégré universitaire de santé et de services sociaux de l'Est-de-l'Île-de-Montréal, Montréal, Québec, Canada; Cécile Le Page Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Alain Lesage Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Olivier Lipp Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Christophe Longpré-Poirier Department of Psychiatry, Université de Montréal, Montréal, Québec, Canada; Sonia Lupien Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Department of Psychiatry and Addictology, Université de Montréal, Montréal, Québec, Canada; Marie-France Marin Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Département de Psychologie, Université du Québec à Montréal, Montréal, Québec, Canada; Carolle Marullo l'Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Jean-Pierre Melun Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Caroline Menard Department of Psychiatry and Neurosciences, Faculty of Medicine, Université Laval, Laval, Québec, Canada; François Noël Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Georges-Frank Pinard Institut

universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Pierrich Plusquellec Faculté des arts et des sciences, École de psychoeducation, Université de Montréal, Montréal, Québec, Canada; Stéphane Potvin Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Department of Psychiatry and Addictology, Université de Montréal, Montréal, Québec, Canada; Ahmed-Jérôme Romain Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Département de Psychologie, Université du Québec à Trois-Rivières, Trois-Rivières, Québec, Canada; Lee Kum Sheung Center for Health and Happiness, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States; Katerine Rousseau Department of Psychiatry and Addictology, Université de Montréal, Montréal, Québec, Canada; Marc Sasseville Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Department of Psychiatry and Addictology, Université de Montréal, Montréal, Québec, Canada; Emmanuel Stip Department of Psychiatry and Addictology, Université de Montréal, Montréal, Québec, Canada; Daniel St-Laurent Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Christo Todorov Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Valérie Tourjman Department of Psychiatry and Addictology, Université de Montréal, Montréal, Québec, Canada; Claudia Trudel-Fitgerald Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Département de Psychologie, Université du Québec à Trois-Rivières, Trois-Rivières, Québec, Canada; Lee Kum Sheung Center for Health and Happiness, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States; Françoise Martha Ulysse Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Andreas Ziegenhorn Department of Psychiatry and Addictology, Université de Montréal, Montréal, Québec, Canada; Vincent Taschereau-Dumouchel Centre de recherche de l'Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada; Department of Psychiatry and Addictology, Université de Montréal, Montréal, Québec, Canada.