

REVIEW ARTICLE

New developments of biofluid-based biomarkers for routine diagnosis and disease trajectories in frontotemporal dementia

Marta del Campo¹ | Henrik Zetterberg^{2,3,4,5,6} | Sam Gandy⁷ | Chiadi U Onyike⁸ |
Fabricio Oliveira⁹ | Chi Udeh-Momoh^{10,11} | Alberto Lleó¹² | Charlotte E. Teunissen¹³ |
Yolande Pijnenburg¹⁴¹Departamento de Ciencias Farmacéuticas y de la Salud, Facultad de Farmacia, Universidad San Pablo-CEU, CEU Universities, Madrid, Spain²Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden³Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden⁴UK Dementia Research Institute at UCL, London, UK⁵Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK⁶Hong Kong Center for Neurodegenerative Diseases, Hong Kong, China⁷Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, New York, USA⁸Division of Geriatric Psychiatry and Neuropsychiatry, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA⁹Department of Neurology and Neurosurgery, Escola Paulista de Medicina, Federal University of São Paulo (UNIFESP), São Paulo, São Paulo, Brazil¹⁰Ageing Epidemiology Research Unit, School of Public Health, Faculty of Medicine, Imperial College London, London, UK¹¹Translational Health Sciences, Faculty of Medicine, University of Bristol, Bristol, UK¹²Neurology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain¹³Neurochemistry Laboratory, Department of Clinical Chemistry, Amsterdam Neuroscience, Amsterdam University Medical Centers, Vrije Universiteit, Amsterdam, the Netherlands¹⁴Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, the Netherlands

Correspondence

Marta del Campo Milan, San Pablo CEU
University, Department of Pharmacy,
Urbanización S/N, 28668, Av. de
Montepríncipe, Alcorcón, Madrid, Spain.
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Abstract

Frontotemporal dementia (FTD) covers a spectrum of neurodegenerative disorders with different phenotypes, genetic backgrounds, and pathological states. Its clinico-pathological diversity challenges the diagnostic process and the execution of clinical trials, calling for specific diagnostic biomarkers of pathologic FTD types. There is also a need for biomarkers that facilitate disease staging, quantification of severity, monitoring in clinics and observational studies, and for evaluation of target engagement and treatment response in clinical trials. This review discusses current FTD biofluid-based biomarker knowledge taking into account the differing applications. The limitations, knowledge gaps, and challenges for the development and implementation of such markers are also examined. Strategies to overcome these hurdles are proposed, including the technologies available, patient cohorts, and collaborative research initiatives. Access to robust and reliable biomarkers that define the exact underlying

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pathophysiological FTD process will meet the needs for specific diagnosis, disease quantitation, clinical monitoring, and treatment development.

1 | BACKGROUND

Frontotemporal dementia (FTD) is the second most prevalent neurodegenerative dementia in young-onset patients (< 65 years old) and has a dramatic effect on life expectancy, with reported survival rates after onset varying from 3 to 14 years.^{1,2} FTD causes a heavy financial burden with costs per patient estimated at two to three times higher for FTD than those for patients suffering from Alzheimer's disease (AD) dementia.^{3,4} FTD is a heterogeneous and complex disorder comprising a wide range of subtypes from a clinical, genetic, and pathological perspective (Figure 1). Based on the clinical phenotype, patients may suffer primarily from behavioral changes and deficits in executive functions (behavioral FTD [bvFTD]) or language disturbances (primary progressive aphasia [PPA]). PPA encompasses semantic variant PPA (svPPA) and non-fluent variant PPA (nfvPPA).^{5,6} A logopenic variant of PPA (lvPPA) has also been described, but is usually associated with AD pathology.^{5,6} The phenotypic spectrum also includes cases with concomitant amyotrophic lateral sclerosis (FTD-ALS),⁷ corticobasal syndrome (CBS),⁸ and progressive supranuclear palsy (PSP; the classic PSP syndrome called Richardson syndrome).⁹ Furthermore, the overlap of clinical features in bvFTD or svPPA with those observed in AD or psychiatric disorders represents additional challenges for clinical diagnosis.^{10–13} These diverse clinical phenotypes can share different pathological and genetic backgrounds (Figure 1), underpinning the complexity of this disorder.

1.1 | FTD neuropathology

FTD is typically associated with focal degeneration of the frontal and temporal cortices, denoted by the term frontotemporal lobar degeneration (FTLD). Microscopically, ~50% of FTLD patients are characterized by aggregates of TAR DNA-binding protein 43 (TDP-43 [FTLD-TDP]) and 45% of FTLD patients develop aggregates of the microtubule-associated protein tau (MAPT, i.e., FTLD-tau). Less commonly (< 5% of the cases), FTLD features aggregates of RNA-binding protein fused in sarcoma (FUS [FTLD-FUS]) or ubiquitin-positive inclu-

sions (FTLD-UPS).^{14–16} Depending on the immunohistochemical profile, that is, density and distribution of the protein aggregates, FTLD-TDP, FTLD-tau, and FTLD-FUS can be subclassified into different subtypes (Figure 1).^{16–19}

1.1.1 | FTLD-TDP

TDP-43 is a nuclear DNA/RNA binding protein that regulates transcription and alternative splicing.^{20,21} Mislocalization and aggregation of this protein in the cytoplasm leads to the pathological stress granules observed in FTLD.²² TDP-43 inclusions are also observed in > 95% of ALS,²² supporting the notion that FTLD-TDP and ALS are part of a clinicopathological continuum.^{18,23} The heterogeneity within TDP-43 histopathological patterns has prompted the definition of five different FTLD-TDP subclassifications (FTLD type A, B, C, D, and E; Figure 1), depending on their shape, distribution, and cellular localization.^{17,24} FTLD-TDP can present with different clinical phenotypes including bvFTD, CBS, or PPA.²⁵ The presence of svPPA and FTD-ALS show a strong correlation with TDP-43 pathology.^{25,26} Recent research suggests that psychiatric symptoms in FTD patients are associated with underlying TDP pathology.²⁷

1.1.2 | FTLD-tau

Misfolded or aggregated tau leads to the formation of pathological intraneuronal inclusion bodies and destabilization of microtubules. Alternative splicing leads to different tau isoforms with three or four microtubule-binding domains (3-repeat [3R] or 4-repeat [4R] tauopathies).²⁸ Based on the predominant tau isoform present in such aggregates (tau 3R, 4R, or 3/4R) and the morphology of the inclusion bodies, FTLD-tau can be classified and subdivided into several neuropathological diagnoses. Thus, FTLD-tau includes Pick's disease (PiD), which features 3R tau pathology, and the 4R tauopathies PSP, corticobasal degeneration, and globular glial tauopathy (GGT; Figure 1).^{18,19} FTLD-tau can also present across the different clinical

phenotypes.¹⁸ Almost half of bvFTD have an underlying FTLD-tau pathology, including PiD and to lesser extent CBD and PSP pathologies. FTLD-tau has also been reported in patients with PPA and CBS phenotypes. The clinical syndrome of PSP highly correlates with PSP tau pathology. In addition, parkinsonism in association with bvFTD or PPA is a predictor of tau pathology.²⁶

1.1.3 | FTLD-FUS/UPS

FUS is also a nuclear DNA/RNA binding protein with diverse functions including transcription regulation, transport of RNA, and cell growth.¹⁶ FUS inclusions are not very common in FTD; still, four different clinico-pathological subclassifications have been proposed.^{29,30} Patients with underlying FTLD-FUS pathology often fulfill the diagnostic criteria of bvFTD.³⁰ Clinically, they are characterized by a disease onset before 40 years, a negative family history, and caudate atrophy on magnetic resonance imaging.³¹

These data highlight that prediction of all these neuropathological subtypes on the basis of clinical phenotype is imperfect and varies across syndromes (Figure 1). Despite some syndromes being highly predictive of a specific underlying pathology (e.g., svPPA or FTD-ALS with TDP or clinical PSP with tau), the most common sporadic bvFTD cases can have different neuropathologies that cannot be predicted by the clinical syndrome.

1.2 | FTD genetics

FTD is highly heritable with approximately 10% to 20% of FTD cases caused by an autosomal dominant mutation.^{32,33} Most of these variants have very poor genotype–phenotype correlations, but they are highly predictive of the underlying neuropathology (Figure 1).^{18,34} The most common genes linked to familial FTD are *MAPT*, progranulin (*GRN*), and chromosome 9 open reading frame 72 (*C9orf72*).^{35–38} We will only focus on these highly penetrant mutations, as exhaustive revisions outlining the heterogeneity of FTD genes have been previously published.^{34,39,40}

1.2.1 | C9orf72

These carriers account for the largest amount of familial cases of FTD, in which abnormal GGGGCC expansions in the non-coding region of the *C9orf72* gene produce toxic RNA foci^{41,42} and dipeptide repeat proteins (DPRs).^{43,44} The number of expansions is directly correlated with pathogenicity, with most confirmed cases bearing hundreds of them.⁴⁰ These carriers mostly present with FTLD-TDP A and B pathology, although type C has also been reported.^{45,46} Clinically, FTD *C9orf72* carriers can present with bvFTD, and in some cases also with PPA.³⁴

1.2.2 | GRN

More than 70 pathogenic mutations of *GRN* have been described, mostly resulting in loss of function either due to aberrant transcrip-

RESEARCH IN CONTEXT

- 1. Systematic Review:** PubMed was used to search, identify, and evaluate the accumulated knowledge in relation to biofluid-based biomarkers for frontotemporal dementia (FTD), together with data gathered through meetings, abstract, and presentations.
- 2. Interpretation:** The findings indicate that FTD clinico-pathological diversity challenges the diagnostic process and the execution of clinical studies and trials, so there is a pressing need for reliable biofluid-based biomarkers for different context of use (e.g., prognosis and diagnosis, monitoring, target engagement, drug efficacy). Among the main limitations and knowledge gaps encountered in the development and implementation of such markers are (a) the clinico-pathological heterogeneity of FTD, (b) the lack of an established definition of the different disease stages of FTD (e.g., preclinical, prodromal, dementia), (c) a better understanding of the similarities and differences between sporadic and familial cases or pathological subclassifications.
- 3. Future Directions:** We propose different strategies to overcome the identified challenges covering not only the study design but also the use of new innovative technologies as well as the importance of patients' cohorts and collaborative research initiatives.

tion or to prevention of translation, which leads to GRN haploinsufficiency in FTD patients.⁴⁰ GRN mutations likely affect lysosomal function in a disease-promoting manner.⁴⁷ GRN carriers often present with FTLD-TDP A pathology and most patients have bvFTD clinical phenotype, though PPA has been also reported in these familial cases.³⁴

1.2.3 | MAPT

Mutations in the *MAPT* gene (with ≥ 40 pathogenic mutations) lead to abnormal forms of the tau protein, promoting its aggregation and interfering with the polymerization and stabilization of microtubules.⁴⁸ These mutations are often associated with PSP and CBD pathology.¹⁸ Genotype-phenotype correlations showed that *MAPT* carriers are associated largely with bvFTD, PPA, and FTD with parkinsonism.³⁴

The clinical, pathological, and genetic complexity of FTD requires the development of biomarkers for the molecular subtypes of FTD. Such biomarkers could be used to increase diagnostic accuracy; quantitate disease staging; and predict, monitor, and measure disease progression.⁴⁹ Depending on the context of use, general biomarkers of FTD or biomarkers for specific FTLD types and subtypes will be needed. Pathology-specific biomarkers are especially relevant to

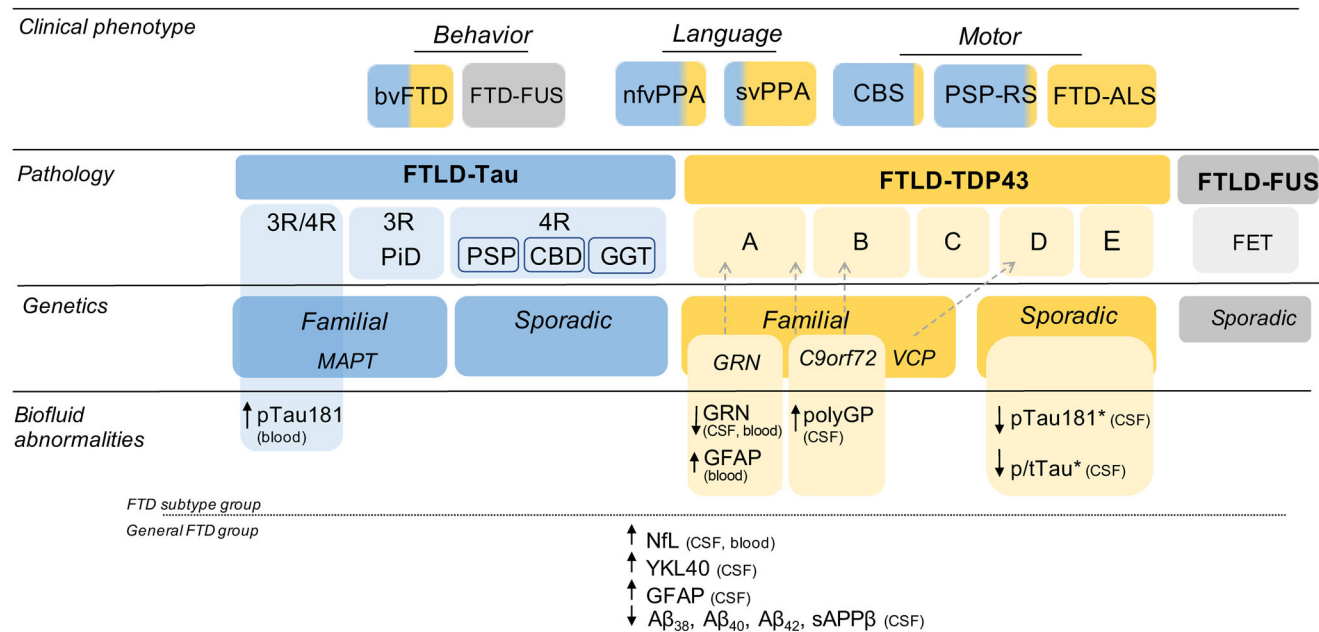


FIGURE 1 Clinicopathological and genetic classification of FTD spectrum. Diagram illustrates the clinicopathological correlations along the FTD spectrum and the corresponding genetic associations. Tau (blue), TDP-43 (yellow), and FET (gray) pathologies, their corresponding immunohistochemical profiles and associated pathological diagnosis are annotated. Genetic forms of FTD are related to specific pathological aggregates (tau or TDP-43). Gray arrows indicate specific associations between genetic mutation and immunohistochemical profiles. The biofluid-based abnormalities indicate biomarkers that are dysregulated either between a specific FTLT subtype (upper panel) or undefined general FTD groups (bottom panel) and controls or between FTLT pathological subtypes (*) in either blood or CSF. Aβ, amyloid beta; bvFTD, behavioral variant frontotemporal dementia; CBD, corticobasal degeneration; CBS, corticobasal syndrome; CSF, cerebrospinal fluid; FET, family of RNA-binding proteins including FUS, Ewing sarcoma and TAF15; FTD, frontotemporal dementia; FTD-FUS, frontotemporal dementia fused in sarcoma variant; FTD-ALS, frontotemporal dementia with concomitant amyotrophic lateral sclerosis; FTLT, frontotemporal lobar degeneration; GFAP, glial fibrillary acidic protein; GGT, globular glial tauopathy; NfL, neurofilament light; nfv, nonfluent variant; PiD, Pick's disease; PPA, primary progressive aphasia; PSP-RS, progressive supranuclear palsy-Richardson's syndrome; p-tau, phosphorylated tau; sv, semantic variant; TDP-43, TAR DNA-binding protein 43 [Correction added on 17 March 2022, after first online publication: Figure 1 has been updated. Some text alignment as well as positioning has been corrected.]

define FTD biologically. Such biomarkers are urgently needed for recruitment for clinical trials, where homogeneous populations of patients with specific FTD pathological subtypes are crucial for testing candidate drugs that target these specific proteinopathies (e.g., tau or TDP).⁵⁰ In clinical trials, biomarkers are also needed to assess target engagement and evaluate drug response. Such markers are very important for FTD treatment development, as the heterogeneity of the clinical presentation prevents the use of clinical or imaging indices as outcome measures.⁵¹ Biofluid-based biomarkers (e.g., cerebrospinal fluid [CSF] and blood) can be especially helpful in clinical practice and clinical trials.^{49–51} CSF has been the most widely used source for the development of fluid biomarkers for neurological disorders because it is viewed as reflecting *ante mortem* biochemical milieu and its changes during the neurodegenerative process, and concentrations of brain pathology-specific proteins are expected to be higher than those measured in blood.⁵² In AD, the implementation of CSF biomarkers in clinical practice has shown enormous benefits for early diagnosis and the testing of new compounds in AD clinical trials.²⁷ Lately, highly sensitive and specific immuno- and mass spectrometry-based approaches have

made blood-based biomarkers feasible—a revolutionary development for AD research.^{53,54} Compared to developments in the AD field, there has been significant progress in FTD biofluid biomarker research in the last 10 years, but this has also encountered difficulties that relate to the relative recency of the key neuropathology discoveries and to the clinical and pathologic heterogeneity of the syndromes. For instance, C9orf72 genetic expansions and the resulting pathological hallmarks were only revealed a decade ago^{35,41–44} and pathological, genetic, and clinical associations have been expanded.^{19,24,27,29,30,45–47} Leveraging these recent and upcoming discoveries warrants further developments within the FTD biomarker field.

Here, we review the key biofluid-based biomarker developments in FTD (Figure 1 and Table 1) and identify the major opportunities and obstacles for the development and implementation in practice and research of biofluid-based biomarkers for FTD. We discuss potential strategies to overcome the obstacles, taking into account the contexts of use, the different methods and technologies available, and the present-day clinical/epidemiological cohorts and collaborative research initiatives.

TABLE 1 Most widely studied biomarkers studies within the FTD field and its context-of-use [Correction added on 17 March 2022, after first online publication: The alignment of table column heads in Table 1 has been corrected.]

Biofluid based biomarker	Context-of-use							Sample matrix	Remarks
	Specific FTD diagnosis			Clinical/genetic/ pathological subtypes	Staging and monitoring	Prognosis	Treatment Response		
	vs. CON	vs. AD	vs. Psych.dis						
Tau, pTau (281/217/231), Aβ42, Aβ40, and their ratios	–	++	ns	+ ^a	ns	ns	ns	CSF/plasma	AD biomarker; co-pathology dependent
pTau181/tTau	–	–	+	+ ^b	ns	ns	ns	CSF	AD biomarkers; limited accuracy
NfL	++	+	++	+	++	++	+	CSF/plasma/serum	General biomarker of neurodegeneration
sAPPβ	+	–	ns	ns	ns	ns	ns	CSF	Specifically decreased in FTD
Progranulin	ns	ns	ns	++ ^c	ns	ns	+	CSF/plasma/serum	Specific genetic subtype
Poly(GP)	ns	ns	ns	++ ^d	–	–	+	CSF	Specific genetic subtype

Abbreviations; ++, validated biomarker (i.e., changes consistently observed across independent studies); +, promising biomarker; –, not useful; A β , amyloid beta; AD, Alzheimer's disease; CON, controls; CSF, cerebrospinal fluid; FTD, frontotemporal dementia; ns, not studied; Psych.dis., psychiatry disorders.

Note: Summary table of the most widely studied biomarkers within the FTD field and their corresponding context-of-use.

^a Logopenic FTD variant.

^b For TDP vs. tau.

^c For GRN mutation carriers.

^d For C9orf72 mutation carriers.

2 | STATE OF THE ART OF BIOFLUID-BASED BIOMARKERS FOR FTD

2.1 | Biomarkers to differentiate FTD from other dementias and non-degenerative disorders

An important challenge for both routine diagnosis and clinical trials is to identify cases within the FTD spectrum and differentiate these from those of related diseases, such as sporadic AD⁵⁵ or the non-neurodegenerative primary psychiatric disorders.⁵⁶ In many AD studies of tau and amyloid beta (A β) fluid biomarkers, FTD has been included as a contrast group. It has been shown that elevated CSF concentrations of total tau (t-tau) and tau phosphorylated at amino acids 181 and, more recently, 217 (p-tau181 and p-tau217, respectively) are surprisingly AD-specific; tau-associated FTD subtypes do not have elevated CSF t-tau and p-tau concentrations,^{57–60} at least not to the levels present in AD.⁶¹ Accordingly, an increased ratio of t-tau or p-tau to the 42 amino acid form of A β (A β 42), i.e., the tau/A β 42 ratio, is an AD-specific finding that separates AD from FTD with high diagnostic accuracies (70% and 86% specificity when analyzing AD vs. bvFTD or svPPA, respectively).⁶² Thus, these biomarkers can be used to identify patients who have frontal lobe dysfunction on the basis of AD pathology, rather than FTD, a condition sometimes called

frontal variant AD.⁶³ Similarly, CSF biomarkers can be useful in the evaluation of the logopenic variant of PPA, which is typically associated with AD pathology, rather than FTD.⁶⁴ In this scenario, the association of elevated CSF tau levels and reduced A β 42/40 ratio, supports AD pathology as the main etiology of the language syndrome.⁶⁴ It has also been repeatedly shown that A β species including A β 38, A β 40, A β 42, and soluble amyloid precursor protein fragment (sAPP β) are lower in CSF from FTD patients than in the compared controls.^{65,66} The reason for this remains unclear, but in AD, cerebral A β pathology is associated with a relatively selective reduction in A β 42 in CSF, while the reduction in FTD is seen for all measurable A β species and the decrease correlates with brain atrophy;⁶⁶ hence, the CSF A β 42/A β 40 ratio works well to differentiate amyloid pathology in AD (with reduced A β 42/40 ratio) from the general reduction of APP-derived peptides often seen in FTD (with A β 42/40 ratio in the normal range, area under the curve [AUC]: 0.85).⁶⁵ Of note, many biomarker studies in FTD may be confounded by co-occurring secondary AD pathology.^{67,68} Therefore, when a patient with an FTD syndrome shows a positive AD CSF biomarker profile it is important to consider all clinical and radiological information to evaluate if the AD pathology is the primary pathology or a comorbid condition. Besides the classical AD CSF biomarkers, several studies have found much higher CSF neurofilament light (NfL, a general biomarker for neurodegeneration) levels in FTD

compared to AD;^{69–72} this finding, particularly in combination with negative AD biomarkers, strongly speaks for a non-AD neurodegenerative disease. For instance, combination of AD CSF biomarkers (A β 42 and p-tau181) with CSF NfL could discriminate FTLT from AD with high performance (AUC > 0.90).⁷³ However, FTD should only be considered in the presence of a compatible clinical syndrome, as CSF NfL levels are increased in multiple related neurodegenerative disorders (e.g., ALS, PSP, multiple system).⁷⁴ For the differentiation between FTD and non-neurodegenerative disorders, several CSF studies showed an excellent performance of NfL for discriminating FTD from psychiatric disorders (AUC > 0.90)^{56,71,75} and consequent perceived added clinical use for the physician.⁷⁶

It is to be noted that the studies described above analyze mainly the performance of classical AD CSF biomarkers and thus are useful to exclude AD pathology rather than to diagnose FTD; or analyze general markers of neurodegeneration (e.g., NfL). These observations highlight the lack of well-established FTD-specific biomarkers. Promising biomarkers have been identified and are being investigated.^{77,78} For example, a study combining CSF NfL, YKL40, and sAPP β measurements from 159 cases with an FTLT-related syndrome yielded high diagnostic accuracies (AUC > 0.90) in discriminating FTD from controls.⁷⁹ While YKL40 is also elevated in other neurodegenerative disorders including AD,^{80,81} sAPP β concentrations were specifically lower in FTLT syndromes.⁷⁹ Similar results were observed in an autopsy-confirmed FTLT cohort.⁸² Other pathways that are currently being examined in the quest for FTD-specific biomarkers include neuroinflammation, lysosomal health, and synaptic health (for a recent review on the topic, please see Swift et al.⁷⁷). Combinations of CSF biomarkers (e.g., NfL, YKL40, p-/t-tau) do not seem to have added value over NfL alone, at least not for the discrimination of FTD from primary psychiatric disorders.⁵⁶

Regarding blood-based biomarkers, recent AD studies showed that plasma concentrations of p-tau181, p-tau217 and p-tau231 are elevated in AD, relative to controls, but not in FTD;^{83–86} the two diseases can thus be separated with close to 100% accuracy using a simple blood test. These promising results were recently confirmed for plasma p-tau181 and p-tau231 in neuropathologically confirmed cohorts.^{84,86} Similar to what was observed in CSF, serum and plasma NfL are elevated in FTD compared to AD, but with limited utility in discriminating FTD from AD.^{87–89} At present, serum NfL has the highest diagnostic accuracy with AUC of up to 0.94 for differentiating FTD from primary psychiatric disorders.^{71,90,91} However, normal NfL levels still do not rule out FTD. Because NfL levels are also associated with disease progression and survival,^{85,92} normal NfL levels are probably associated with slowly progressive phenotypes of FTD.

2.2 | Biomarkers to define the underlying proteinopathies

Biomarkers for specific FTD-related proteinopathies (TDP-43, tau, or FUS^{14,15}) are a pressing need for drug development strategies that

focus on specific pathological processes. Several independent studies have shown that CSF p-tau/t-tau ratio demarcate FTD-TDP patients from FTD-tau cases with sensitivity and specificity values around 82% and 62%, respectively.^{93–97} Other studies have shown that the value of CSF tau measurements is limited to pure cases of FTLT (e.g., without copathologies).^{67,61} Lower CSF p-tau could discriminate FTD-TDP from FTD-tau in sporadic pure FTD cases after excluding AD.⁶⁷ As CSF t-tau levels are not strongly associated with underlying FTLT-tau, it would be worthwhile to study CSF pathological tau isoforms in more detail.⁹⁸

While it is possible to measure TDP-43 in biofluids, current assays do not differentiate normal from pathological TDP-43.⁹⁹ A recent study using real time quaking-induced conversion assay, a test based on the amplification of misfolded proteins and used for detection of prion proteins, showed in vitro TDP-43 aggregate formation in CSF.¹⁰⁰ In a recent proof-of-concept small clinical study this assay discriminated FTD and ALS patients from controls with 94% sensitivity and 85% specificity.¹⁰⁰ These studies await independent replication. However, the seed-based testing paradigm may help to develop additional assays for inclusion-specific forms of TDP-43. Biomarkers that reflect metabolic changes downstream of TDP-43 pathology might also be developed.

As far as we are aware, there is no biomarker of FUS pathology available. Ideally, a combined panel measuring markers of tau, TDP-43, and FUS would allow for accurate pathologic diagnosis of FTD, but these have so far posed important challenges. Some studies have analyzed well-established biomarkers that are not directly related to the specific proteinopathy. For example, higher levels of both CSF and plasma NfL have been observed in FTD-TDP than in FTD-tau cases, but with high within-group variability.^{87,101,102} Non-hypothesis driven proteomics studies have identified multiple proteins that are differentially expressed in FTLT neuropathological or genetic subtypes.^{95,103,104} These unbiased approaches have the potential to facilitate the identification of biomarkers specific for the main pathophysiological processes associated with the FTD subtypes (e.g., lysosomal degradation, autophagy). Replication and validation of these findings are of utmost importance to move the field forward.

2.3 | Biomarkers for target engagement and treatment monitoring

Low CSF and blood progranulin levels have been found in GRN mutation carriers with an almost 100% diagnostic accuracy.^{105–107} It is expected that disease-modifying treatments aimed at restoring progranulin deficits can be evaluated by these serum GRN measurements. In C9orf72 expansion carriers, poly(GP), one of the DPR proteins produced by the C9orf72 expansions, is elevated as early as the presymptomatic phase.^{108–110} Thus, DPR proteins may prove useful as pharmacodynamic biomarkers in gene-silencing studies. While blood NfL has promise for measuring treatment effects in different neurodegenerative disorders,^{51,92,111,112} its utility as an endpoint measure

in *GRN* carriers appears to be limited by the observed longitudinal fluctuations.⁹²

2.4 | Biomarkers for disease staging and prognosis

As observed in other dementias, accelerated rates of decline have been quantified during the symptomatic phase of both familial and sporadic FTD using clinical and imaging measures¹¹³ and thus, markers reflecting the disease stage independent of the clinicopathological presentation would be desirable. Several studies have already indicated that baseline NfL concentrations in both CSF and blood could reflect the aggressiveness of the disease as it can predict rate of disease progression in the different clinicopathological phenotypes in both sporadic and familial FTD.^{87,96,114–117} Future studies will clarify whether baseline CSF NfL levels can be used to stratify FTD severity (e.g., low, intermediate, high). Longitudinal analysis of CSF NfL shows that the levels of this marker change little during the symptomatic phase of FTD in individual patients.¹¹⁴ However, a recent longitudinal multicenter study of familial FTD has shown in symptomatic *GRN* mutations carriers a rise in serum NfL levels as illness duration time and severity increased, notable from symptom onset on but with substantial fluctuations in the individual NfL trajectories.⁹² Importantly, the study also showed that serum NfL levels increase in presymptomatic carriers 1 to 2 years before symptom onset. The study was limited by the number of FTD mutation carriers undergoing conversion to symptomatic phase ($n = 9$); nevertheless, it suggests that baseline serum NfL levels may discriminate those in the transition from normal to symptomatic status (i.e., converters) from those that are not in transition (i.e., non-converters) with good accuracy,⁹² indicating a potential utility of serum NfL as a prognostic marker and a selection criterion for clinical trials, at least in familial cases. Recent findings observed that higher levels of plasma glial fibrillary acidic protein (GFAP), an astrogliosis marker, was associated with a greater decrease in Mini-Mental State Examination score and a poor cognitive outcome in both FTD and AD. Thus, in combination with FTD-specific markers, plasma GFAP could also be potentially used to track disease severity or predict greater cognitive decline.¹¹⁸

3 | GAPS AND LIMITATIONS ON THE DEVELOPMENT OF BIOFLUID-BASED BIOMARKERS FOR FTD

Taken together, except for NfL, the most robust FTD biofluid-based biomarkers developed from the scientific efforts of the last decade are related to AD pathology rather than that of FTD. The high pathologic heterogeneity of FTD is a particular challenge; the current biomarkers are not specific for any pathologic subtype, and biomarkers may have different utilities depending on the FTD subtype.

3.1 | Challenges in the development of biomarkers for specific diagnosis of FTD and its pathological subtypes

Given the high heterogeneity of FTD, it is not to be expected that a single FTD-specific biofluid marker will be used to differentiate FTD from other neurodegenerative or non-neurodegenerative disorders. Inclusion of non-FTD dementias (e.g., AD) in biomarker studies will facilitate the distinction of FTD-specific changes from those that are common to all neurodegenerative states. The fact that concomitant AD is not uncommon in FTD adds further complexity.⁶⁸ It will be important, therefore, to evaluate the effects of concomitant AD pathology in FTD biomarker studies, using standard AD CSF (and more recently also plasma) biomarkers.^{67,68,83}

The identification of biofluid-based biomarkers that discriminate FTD pathologies (TDP-43, tau, FUS), has often been hindered by the availability of pathologically characterized samples with known underlying pathology—these are usually selected based on autopsy confirmation or genetic mutation status (e.g., *C9orf72* and *GRN* for TDP-43 or *MAPT* for tau^{18,35,37,22}). The scarcity of these samples has prompted efforts to enrich cohorts with FTD syndromes that are highly correlated with a specific underlying neuropathology (e.g., FTD-ALS for FTLD-TDP²² or PSP and CBS for FTLD-tau^{119,120}) and/or to jointly analyze data from both combined cohorts of sporadic and familial cases with the same neuropathology background. It must be noted, however, that recent neuropathological studies have reported TDP-43 copathology in a considerable amount of FTLD-tau-related syndromes such as CBD, and to lesser extent PSP.¹²¹ In addition, it is not clear to what extent the biochemical changes in those cases with FTD mutations resemble those of sporadic cases with the same proteinopathy, nor across the different immunohistochemical profiles within each pathological subtype (e.g., tau: 3R, 4R, 3R/4R; TDP: A, B, C, D, and E). Pathophysiological differences between hereditary and sporadic FTD have been reported.^{122,123} Recent studies have shown that the performance of CSF p-tau181 to discriminate between FTD pathological subtypes (i.e., FTLD-tau vs. FTLD-TDP) was considerably reduced when mutation carriers were analyzed separately (AUCs of 0.87 in sporadic pure cases vs. 0.58 in genetic cases).^{67,61} Similarly, the levels of plasma p-tau181 were approximately 2-fold increased in *MAPT* mutation carriers with mixed 3/4R but not in those with 4R tau pathology.⁸³ Recent findings have shown that the levels of plasma GFAP are increased in symptomatic *GRN* carriers but not in those with *C9orf72* expansions or *MAPT* mutations, and could distinguish these genetic forms with AUCs >0.70.¹²⁴ Furthermore, findings from molecular studies indicate that the mechanisms underlying TDP-43 aggregation by *C9orf72* expansions differ from those driven by *GRN* loss of function.^{125,126} Taken together, these observations indicate a high heterogeneity also within each pathological and genetic subtype, in which different biological processes underlying familial and sporadic cases may ultimately result in similar proteinopathy profiles—but not necessarily in similar biomarker profiles. In other words, within a proteinopathy class

different mechanisms may generate different biochemical profiles in body fluids, especially in the early stages of the disease. The biological complexity of FTLT subtypes needs to be considered in the design and interpretation of FTD biomarker studies.

3.2 | Challenges in the development of biomarkers for disease stage, prognosis, and drug efficacy

Biofluid-based biomarkers for the different stages of FTD, including the preclinical and prodromal phases, are still needed. This is especially challenging in FTD as, unlike in AD, there is still not an established definition of the preclinical/prodromal stages (e.g., mild cognitive impairment due to FTD). Diagnosis is typically delayed for up to 6 years.¹⁰⁰ Moreover, the first and core symptom of FTD is a deficit in social cognition, which is not readily recognized as such until the illness is well established. The construct of social cognition, including emotion recognition, theory of mind, empathy, and moral reasoning, has been proven difficult to measure in clinical practice.⁷¹ Use of newly developed psychometric measures for characterizing all stages of symptoms (e.g., FTLT-Clinical Dementia Rating, Multidomain Impairment Rating) in familial FTD research will facilitate the discovery and validation of early FTD biomarkers.^{51,127} As highlighted above, the identification of early diagnostic markers will likely be more effective when accounting for the pathological heterogeneity of the disease.

A major challenge in the field of neurodegenerative dementias is to predict whether and when an individual will develop the specific disease, an important question as early application is expected to increase the value and efficacy of treatments aiming to prevent or delay disease progression. Because disease progression in most neurodegenerative diseases is non-linear, longitudinal studies characterizing the behavior of a biomarker over time should include at least three time points.¹²⁸ In this respect, blood-based biomarkers are more suitable than CSF biomarkers. Considering the lack of preclinical/prodromal markers for sporadic FTD, studies of familial FTD are crucial for such purposes. The utility of serum NFL as prognostic marker should be replicated in larger cohorts,⁹² analyzing also the potential influence of the different FTD genetic backgrounds. It is also essential to understand whether findings from familial FTD research can be generalized to sporadic FTD. These data also indicate that biochemical changes can be detected in blood before the appearance of clinical symptoms, and it thus boosts the search for additional biomarker candidates. Despite the need for more studies, it should be noted that the presymptomatic phase of FTD, at least in familial cases, might be shorter than that observed in familial forms of AD; as in the latter, NFL changes were observed already 10 years before symptom onset.¹²⁹ Considering that serum NFL is also a general marker of neurodegeneration with similar NFL changes in presymptomatic familial AD cases,¹²⁹ the quest for predictive biomarkers specific for FTD especially in sporadic cases is warranted.

To date, there are no established biomarkers to measure target engagement or drug efficacy in FTD clinical trials, especially for sporadic cases. The increasing number of trials in the industry pipeline

accentuates the need to develop markers for different contexts of use that account for the clinical and pathologic diversity of FTD.⁵¹

4 | FILLING THE GAPS ON THE DEVELOPMENT OF BIOFLUID-BASED BIOMARKERS FOR FTD

4.1 | Emerging technologies and approaches

The identification of novel biomarkers will be facilitated by leveraging a variety of technologies. Mass spectrometry (MS) has the advantage of an unbiased screening, which has facilitated the identification of novel biomarkers for FTLT subtypes.^{103,104} Novel proteins identified through MS approaches can then be measured as single analytes using immunoassays or incorporated into panels of protein arrays for further validation studies.^{95,103,104,130,131} Conventional unbiased MS methods are, unfortunately, still not optimal for blood proteomic analysis. This limitation is partially overcome by novel and highly sensitive high-throughput protein arrays, such as aptamer-based technologies, immunobased proximity extension assays, or antibody suspension beads arrays, which can readily measure large sets of protein libraries in CSF and blood samples.^{132–138} An additional advantage of such protein arrays is that the reagents used for biomarker discovery with specific protein binders (e.g., antibodies) can in principle be also used for validation, and for translation to the clinical setting in which immunoassays are a cornerstone of clinical chemistry analyses.^{52,139} The different proteome profiling technologies currently available can be useful to cross-validate findings, an essential step toward the development of optimal biomarkers. It is, however, expected that these technologies will also complement each other as protein libraries partially differ, and the distinct platforms can detect the proteins in different conformation/states (denatured in MS vs. native in protein arrays).

It is also conceivable that the search should be continued in alternative matrices or alternative targets, such as RNA in platelets or extracellular vesicles. Blood platelet mRNA analysis has shown potential for multiple sclerosis.¹⁴⁰ Panels (proteins, nRNA, metabolites) may be needed to capture the full complexity of the pathological differences among the FTD subtypes, and within them, and thus multiplex technologies and computer assisted algorithms need to be used. These could be extended or incorporated into multimodal approaches that include not only biofluid-based biomarkers (e.g., CSF and blood), but also other types of measures (e.g., imaging results, genetic variation, neuropsychological findings, etc.), which can be especially helpful for both clinical practice and trials.^{49,51}

4.2 | Collaborative initiatives

The identification of biofluid-based biomarkers for FTD pathologies will require the analysis of data and samples from large and well-characterized cohorts with longitudinal and autopsy-confirmed cases. Study design and analyses should account for the potential influence of specific mutations or pathological subclassifications, especially within

the earliest stages of the disease. This would also involve more systematic *post mortem* research in FTD, together with deep phenotyping. Considering the limited availability of highly characterized samples, such studies will only be successful when multiple centers are involved. The extension of existing cohorts and development of new ones will be extremely valuable and, therefore, there is a need to reinforce the interest and engagement of the advocacy community, patients and families, and the public in FTD research.

Several initiatives have facilitated collaborative studies worldwide, including the Genetic Frontotemporal Dementia Initiative (GENFI), the ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD), and their coming together in the worldwide FTD Prevention Initiative (FPI). These consortia are continuously gathering invaluable information from multiple FTD cohorts worldwide and are the reference for many of the FTD biomarker studies performed to date, especially in familial FTD. The FTD professional interest area (FTD-PIA) has been recently created within the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART), which is collaborating with the biofluid-based biomarkers PIA (BBB-PIA) to facilitate the development and optimization of biomarkers for FTD.

For validation and implementation of the identified markers, the field can leverage the developments from more advanced fields, such as the AD field. This especially applies to preanalytical aspects and the development of standard operating procedures for sample handling and analysis, such as for AD biomarkers in CSF and blood,^{141–144} and to quality control programs,¹⁴⁵ which are a requirement for *in vitro* diagnostic tests. These activities are promoted through different organizations such as the Society for CSF Analysis and Clinical Neurochemistry or the Global Biomarkers Standardization Consortium (GBSC). Moreover, there is a potential for synergism from initiatives to obtain regulatory approval and reimbursement for, for example, NfL for other diseases.

4.3 | Understanding the cautions and caveats in the development of FTD biofluid-based biomarkers

It is valuable to specify some of the potential pitfalls and shortcomings when biofluid-based biomarkers are translated from the level of discovery and research to that of clinical dogma. Many of these points will be well known to the experts but perhaps less so to others not familiar with biomarker-based diagnosis and staging of neurodegenerative diseases. Reflection on the state-of-the-art reveals both “known unknowns” and “unknown unknowns.” Examples of some of the known unknowns are the potential contributions of vascular and immune mechanisms as we contemplate the full picture from disease initiation to disease progression. Vascular and immunological mechanisms have been proposed for many neurodegenerative diseases and, for some, have been demonstrated to play key roles in the development and progression of clinical syndromes. Even when, for example, vascular and/or immune factors have been implicated, there is insufficient knowledge about which biomarkers can be combined to give a more complete pic-

ture. For vascular and immunological abnormalities, reliable biomarkers are infrequent, imprecise, or lacking altogether. Besides the imprecision that this brings to nosology, the complexity of multiple concurrent pathologies will certainly hamper the ability to test interventions that are aimed at only one component of the concurrent pathologies. In other words, the more complex the concurrent pathologies, the greater the challenge in designing trials that are sufficiently sensitive to generate interpretable clinical or biomarker endpoints. It is also worth noting that age-, sex-, race-, and ethnicity-based variations; the frequency of comorbidities; and the effects of genetic diversity must always be kept in mind, as observed already in AD and ALS,^{146–157} but also within the FTD field.^{158–160} Indeed, it is far more prudent to assume that these parameters are more likely to be important than to dismiss them.

The unknown category is illustrated by the proliferation of newly recognized clinicopathological entities. For example, primary aging-related tauopathy (PART), limbic age-related TDP-43 encephalopathy (LATE), and hippocampal sclerosis may be associated with amnesic syndromes that are only slowly progressive and may be associated clinically with a “chronic mild cognitive impairment.” Slow progression syndromes have the potential to confound the interpretation of biomarker characterizations and clinical trial outcomes when they are misclassified in studies as examples of typical cases. It is therefore important to acquire the genetic, biofluid, and neuroimaging panels that will facilitate the characterization and classification of atypical proteinopathies and the syndromes with which they are associated. While biomarker-based diagnosis has made a quantum leap forward in the past decade, there remain important caveats as they are translated from the research setting into more general application in clinics worldwide.

5 | CONCLUSIONS AND FUTURE DIRECTIONS

In current clinical practice, the place of CSF analysis is to exclude AD pathology and verify neurodegeneration—it does not have utility for affirmative diagnosis of FTD.⁵ The blood-based biomarker NfL is now being incorporated in clinical practice for FTD, especially to differentiate bvFTD from primary psychiatric disorders.^{71,76} Several novel biomarker candidates reflecting different pathological processes associated with FTD beyond the classical proteinopathies have been identified (lysosomal markers, inflammatory markers, circulating nucleic acids, synaptic markers),⁷⁷ and are in need of thorough validation in well characterized independent cohorts of familial and sporadic FTD. There is a need to identify and validate biomarkers for different purposes (differential diagnosis, pathology typing, staging, prognostication, treatment monitoring) using robust approaches that allow their incorporation into clinical diagnostic criteria. It is expected that the technical developments of the last years (e.g., ultrasensitive technologies, large high-throughput protein panels) will facilitate such developments. CSF biomarker research is still essential to support the association of the different markers with pathophysiological processes, but translation into blood-based biomarkers would be ideal for repeated measurement in longitudinal studies and broad use, eventually, in

practice. The high complexity and heterogeneity of FTD discourages the use of small sample sizes in biomarker analyses and calls for collaborative large multicohort studies with thoroughly characterized samples (i.e., with carefully ascertained and measured clinical, genetic, and pathological indices). A fuller understanding of the molecular factors and biomarkers that underlie FTD pathophysiology at different stages of the disease will optimize clinical and molecular diagnosis and provide an invaluable resource for the development and testing of novel therapies.

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CONFLICTS OF INTEREST

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