



OPEN ACCESS

EDITED BY

K. Ray Chaudhuri,
King's College Hospital, Dubai,
United Arab Emirates

REVIEWED BY

Maurizio Giustetto,
University of Turin, Italy
Violeta Belickienė,
Lithuanian University of Health
Sciences, Lithuania

*CORRESPONDENCE

Petra Bago Rožanković
✉ pbago0501@gmail.com

RECEIVED 21 March 2026

REVISED 16 May 2026

ACCEPTED 20 May 2026

PUBLISHED 13 July 2026

CITATION

Bago Rožanković P and Šimić G (2026)
Emerging biomarkers for Parkinson's
disease in biological fluids.
Front. Aging Neurosci. 18:1835751.
doi: 10.3389/fnagi.2026.1835751

COPYRIGHT

© 2026 Bago Rožanković and Šimić. This
is an open-access article distributed
under the terms of the [Creative
Commons Attribution License \(CC BY\)](#).
The use, distribution or reproduction in
other forums is permitted, provided the
original author(s) and the copyright
owner(s) are credited and that the
original publication in this journal is
cited, in accordance with accepted
academic practice. No use, distribution
or reproduction is permitted which does
not comply with these terms.

Emerging biomarkers for Parkinson's disease in biological fluids

Petra Bago Rožanković^{1,2*} and Goran Šimić³

¹Department of Neurology, University Hospital Dubrava, Avenija Gojka Šuška, Zagreb, Croatia, ²School of Medicine, Catholic University of Croatia, Ilica, Zagreb, Croatia, ³Department of Neuroscience, Croatian Institute for Brain Research, University of Zagreb School of Medicine, Šalata, Zagreb, Croatia

Early and accurate diagnosis of Parkinson's disease (PD) remains a challenge, hindering the efficient recruitment of patients into clinical trials aimed at disease modification. This underscores the urgent need for validated and clinically applicable biomarkers. Research continues to expand our knowledge of fluid biomarkers for detecting and monitoring PD progression. Cerebrospinal fluid α -synuclein (α -syn) seed amplification assays (SAA) have emerged as highly sensitive and specific biomarkers for the diagnosis of PD. The development of less invasive procedures using biological fluids such as serum or saliva would be more practical for routine clinical use. Recent data demonstrate the presence of pathogenic α -synuclein in the serum of PD patients compared with healthy controls, detected using real-time quaking-induced conversion (RT-QulC) assays. Elevated ratios of pS129- α -syn and/or oligomeric α -syn to total α -syn have also been reported in PD. Future research should clarify differences in protein aggregate formation across various synucleinopathies. Promising advances toward a clinically useful blood-based diagnostic test for PD include the quantification of proteins released from neural-derived extracellular vesicles (NDEVs), such as oligomeric and phosphorylated α -syn, tau, and disease-associated microRNAs. Given the role of neuroinflammation in PD pathogenesis, inflammatory biomarkers, including interleukin (IL)-6, IL-10, tumor necrosis factor- α (TNF- α), glial fibrillary acidic protein (GFAP), chitinase-3-like protein 1 (YKL-40), and monocyte chemoattractant protein-1 (MCP-1), are under active investigation. Furthermore, fluid biomarkers associated with Alzheimer's disease pathology are being explored for their potential to predict motor and cognitive decline in PD and related synucleinopathies. Salivary EVs hold promise as a non-invasive source of PD biomarkers; however, robust validation in large, well-characterized cohorts is essential to improve the diagnostic and prognostic accuracy of PD.

KEYWORDS

Alzheimer's disease biomarkers, extracellular vesicles, neuroinflammation, Parkinson's disease, seed amplification assays (SAA), α -synuclein

1 Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by core motor and non-motor symptoms, as defined by current diagnostic criteria (Lee and Gilbert, 2016; Postuma et al., 2015). However, these clinical features overlap with other atypical or secondary parkinsonian syndromes, leading to misdiagnosis in up to 20% of cases (Rizzo et al., 2016). This emphasizes the need for reliable, clinically applicable biomarkers of PD to optimize diagnosis and treatment development.

A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Biomarkers are used for diagnosis, evaluation of disease severity and prognosis, and prediction of responsiveness to therapeutic intervention. Various factors could be considered biomarkers, including clinical signs, biochemical specimens, imaging findings, and genetic data (Biomarkers Definitions Working Group, 2001).

This review provides a distinct perspective by integrating evidence from α -synuclein (α -syn) seed amplification assays (SAA) with extracellular vesicle (EV) cargo across multiple biofluids, with a special focus on saliva-derived vesicles. It discusses methodological pitfalls, cross-cohort reproducibility, and the translational path toward clinically useful multi-marker panels. We explicitly call out gaps in the literature: limited standardization of saliva EV isolation/analysis, insufficient longitudinal data linking salivary EV cargo to clinical trajectories, and the need for head-to-head comparisons of EV sources from saliva, plasma, and neuron-derived EVs (NDEVs) within the same cohorts. Here, by standardization, we mean the adoption of widely accepted guidelines, procedures, and consensus protocols such as those recommended for Minimal Information for Studies of Extracellular Vesicles (MISEV, Welsh et al., 2024; for review see Guzowska et al., 2026), which would include cargo normalization (e.g., relative to vesicle number, total protein, or neuron-enriched markers) and commercially available kits and assay platforms that are scalable and cost-effective for clinical use, to achieve consistent and comparable results across different laboratories.

Biomarkers with the potential to detect the early stages of PD or differentiate it from other parkinsonian disorders could contribute to better patient recruitment in clinical trials targeting disease modification. Furthermore, reliable biomarkers could contribute to more accurate disease prognosis and assessment of treatment response in clinical trials (Delenclos et al., 2016).

In recent years, research on biomarkers in biological fluids has expanded, providing new data for the diagnosis of PD. Cerebrospinal fluid (CSF) α -syn SAA have been validated as highly sensitive and specific biomarkers for PD diagnosis (Koga et al., 2021; Kang et al., 2019; Russo et al., 2021; Bellomo et al., 2022; Siderowf et al., 2023; Grossauer et al., 2023; Poggiolini et al., 2022). In distinguishing PD from other disorders, serum α -syn levels, including total, phosphorylated, and oligomeric variants, have been measured using real-time quaking-induced conversion (RT-QuIC) assays (Rossi et al., 2020; Okuzumi et al., 2023; Pedersen et al., 2025; Stuendl et al., 2021; Parnetti et al., 2019; Zubelzu et al., 2022). However, further reliable quantifications and identification of specific pathological patterns of α -syn aggregates are needed to distinguish different synucleinopathies (Ganguly et al., 2021). Promising advances include the quantification of α -syn variants, tau protein, and disease-associated microRNAs from neuron-derived extracellular vesicles (NDEVs) (Jiang et al., 2020; Zhao and Yang, 2021; Xylaki et al., 2023; Ohmichi et al., 2019; Si et al., 2019; Niu et al., 2020; Ma et al., 2025). Additionally, inflammatory biomarkers and those associated with Alzheimer's disease (AD) have been explored for their potential in diagnosing PD (Coughlin and Irwin, 2023; Zimmerman and Brockman, 2022; Lin et al., 2025).

This review summarizes current knowledge of specific biomarkers for PD in biological fluids, with a special emphasis on their roles in early diagnosis and disease progression.

2 Alpha-synuclein biomarkers

Alpha-synuclein (α -syn) misfolding plays a central role in the pathogenesis of PD. Post-translational modifications, such as phosphorylation of α -syn, and the facilitation of misfolding of α -syn by various processes, including genetic mutations, oxidative stress, and impaired function of the ubiquitin-proteasome system, result in the formation of oligomeric forms, insoluble fibrils, and ultimately Lewy bodies, a pathological hallmark of PD (Li X. Y. et al., 2021; Poewe et al., 2017; Schmid et al., 2013). Therefore, levels of total, phosphorylated, and oligomeric α -syn have been evaluated as potential biomarkers in PD diagnosis, disease monitoring, and clinical trial design.

2.1 Early diagnosis of PD and differentiation from other disorders

2.1.1 Total alpha-synuclein

Clinical heterogeneity among enrolled patients and methodological differences contribute to the limited diagnostic accuracy of measuring CSF total α -syn (t - α -syn), with low potential to differentiate PD from other neurodegenerative disorders (Førland et al., 2020; Schulz et al., 2021; Foulds et al., 2012; Twohig et al., 2018; Magdalinou et al., 2015; Mollenhauer et al., 2017; Goldman et al., 2018; Abdi et al., 2021; Zhou et al., 2015). Evaluation of t - α -syn in plasma, serum, or saliva as a biomarker for PD diagnosis has yielded conflicting results (De Bartolo et al., 2023; Chahine et al., 2020; Youssef et al., 2021). These findings reflect a high inter-study variability due to *inadequate control for pre-analytical factors* (sampling protocols, CSF blood contamination), *lack of standardized quantification methods* (assays, antibodies), and *unaddressed clinical heterogeneity* (disease stage, control group variability), leading to insufficient sensitivity and specificity (Ganguly et al., 2021; Hatano et al., 2024). A meta-analysis of 32 studies found a significant increase in plasma/serum t - α -syn levels in PD patients compared with healthy controls, with a stronger effect observed in the early stages of the disease (Zubelzu et al., 2022). Quantitative evaluation of plasma/serum α -syn levels has been performed using monoclonal antibodies coupled with magnetic nanoparticles, showing that both plasma and serum α -syn levels were higher in PD patients than in healthy controls (Chang et al., 2020). Recently introduced α -syn seed amplification assays (SAA) have shown high sensitivity (>95%) and specificity (98%) in detecting pathological α -syn aggregates (Rossi et al., 2020; Groveman et al., 2018). This approach is based on the ability of α -syn seeds to induce the formation of pathogenic oligomeric and fibrillary α -syn using real-time quaking-induced conversion (RT-QuIC) and protein misfolding cyclic amplification (PMCA) methods, as shown in Figure 1. (Fairfoul et al., 2016;

Poggiolini et al., 2022; Wang et al., 2022). Results from a cross-sectional study evaluating CSF α -syn SAAs in a large cohort of 1,123 subjects demonstrated their feasibility in detecting PD compared to healthy controls (sensitivity 88%, specificity 96.3%) (Siderowf et al., 2023). Additionally, a positive CSF α -syn SAA result was found in 88% of subjects with hyposmia or rapid eye movement (REM) behavior disorder (RBD), suggesting its potential use in detecting the prodromal stage of PD (Siderowf et al., 2023). Positive CSF α -syn SAA results are more common in subjects at risk for PD, with the highest sensitivity observed in patients with glucocerebrosidase (*GBA1*) variants (96%) and the lowest in those with leucine-rich repeat kinase 2 (*LRRK2* Gly1920Ser) variants (68%) (Siderowf et al., 2023). Several other studies have also reported lower rates of positive α -syn SAA results in PD patients with *LRRK2* variants compared with those with *GBA1* variants (Rossi et al., 2020; Garrido et al., 2019; Brockmann et al., 2021). Additionally, CSF α -syn SAA results were negative in patients with *PRKN* and *PINK1* variants. Together with findings that these forms are associated with little or no Lewy body pathological changes, it has been suggested that CSF α -syn SAA may be more useful in PD with pronounced α -syn pathology (Brockmann et al., 2021; Pouloupoulos et al., 2012; Henderson et al., 2019). This marker could help differentiate PD from progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), but with lower accuracy in differentiating PD from multiple system atrophy (MSA) (Grossauer et al., 2023; Wang et al., 2012). Recently, α -syn SAA activity has been classified based on signal intensity and association with different pathologies, showing specificity of 87% for MSA, 97% for PD, and 100% for idiopathic RBD (Ma et al., 2024; Wang et al., 2022).

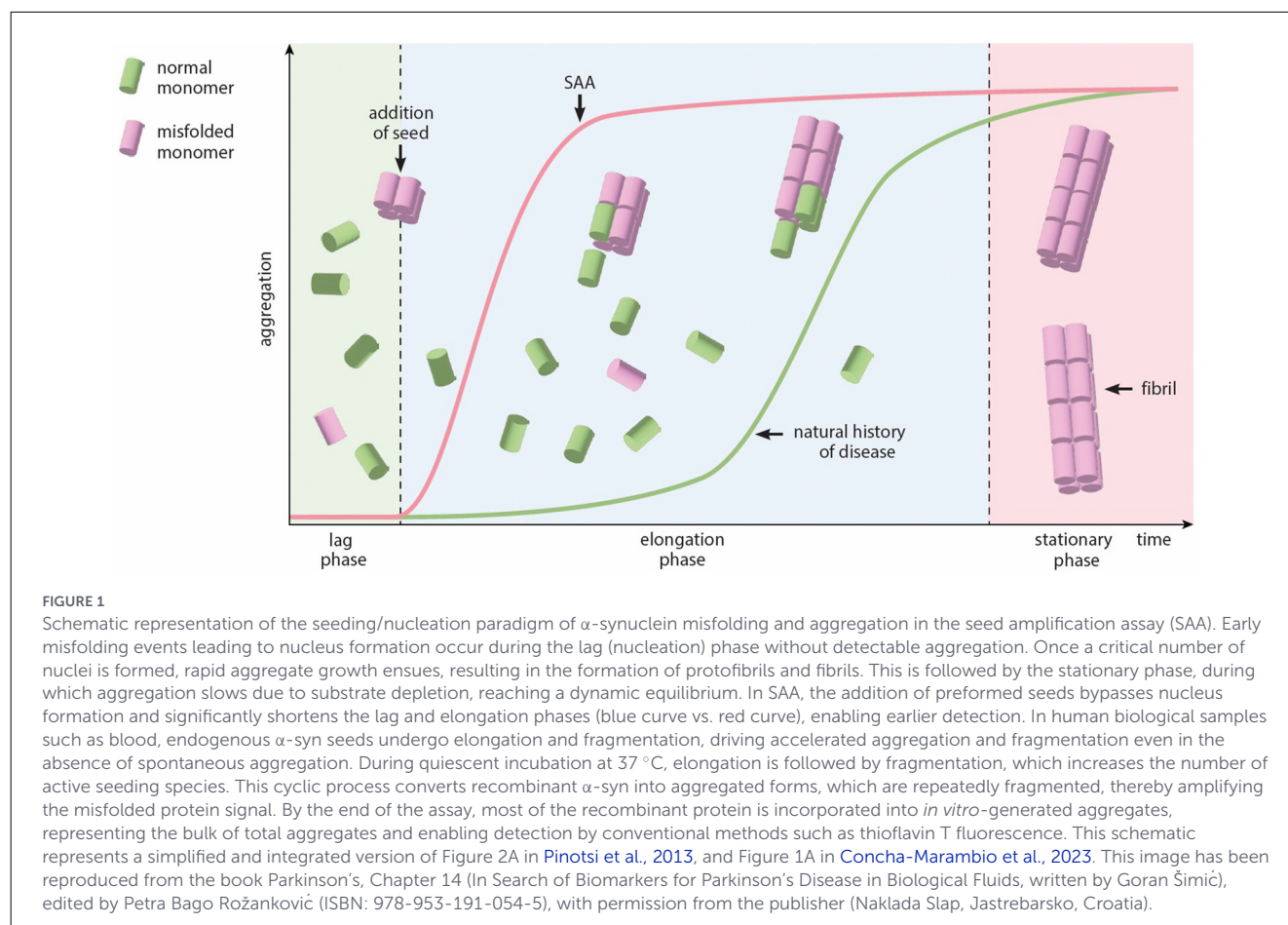
A positive serum α -syn SAA result was found in all PD patients, even 1–10 years before clinical diagnosis, compared to negative SAA results in healthy controls (Kluge et al., 2024). In another study, plasma α -syn levels were significantly higher in PD patients than in healthy controls, with higher levels observed in patients with PD dementia (PDD) compared with those with mild cognitive impairment in PD (PD-MCI) or PD with normal cognition (Lin et al., 2017). Using the combined RT-QuIC technique with immunoprecipitation (IP/RT-QuIC), Okuzumi and colleagues evaluated the presence of α -syn in serum, reporting positive results in 95% of patients with PD, 90% of patients with dementia with Lewy bodies (DLB), and 44% of patients with RBD (Okuzumi et al., 2023). A recent study evaluating α -syn SAA in tear fluid reported positive results in 55% of PD patients, consistent with findings obtained from CSF (Canaslan et al., 2026). Results from several studies show that salivary t - α -syn levels are significantly lower in patients with PD than in healthy controls, while others failed to confirm these findings (Al-Nimer et al., 2014; Sabaei et al., 2023; Shaheen et al., 2020; Vivacqua et al., 2016, 2019). Wang et al. performed a prospective study on serum and saliva samples of PD patients and healthy controls using α -syn - SAA analyses, demonstrating high sensitivity (95.83%), specificity (96.15%), and accuracy (0.98) of combined serum and saliva α -syn-SAA with a potential for accurate PD diagnosis in clinical practice (Wang et al., 2024). Measuring t - α -syn alone cannot discriminate between physiological and pathological forms. In a healthy state, α -syn is present in high amounts in monomeric or tetrameric

forms, which, during the neurodegenerative process, transform into pathogenic conformations, including oligomers and fibrils, post-translational modifications such as phosphorylated forms, or α -syn localization within exosomes (Giampa et al., 2021; Oueslati, 2016).

2.1.2 Pathogenic forms of alpha-synuclein

Modification of physiological α -syn proteins into misfolded oligomeric forms represents a dominant pathological change in PD (Oueslati et al., 2010). Most studies show increased levels of oligomeric forms of α -syn (o - α -syn) and an increased o - α -syn/ t - α -syn ratio in the CSF of PD patients compared to non-PD subjects (Tokuda et al., 2010; Hansson et al., 2014; Park et al., 2011; Cariulo et al., 2019; Majbour et al., 2016). Levels of o - α -syn are also increased in other fluids, including plasma (El-Agnaf et al., 2006; Duran et al., 2010), saliva and tears (De Bartolo et al., 2023; Kang et al., 2016; Vivacqua et al., 2019; Devic et al., 2011; Kharel et al., 2022; Hamm-Alvarez et al., 2019; Maass et al., 2020) and red blood cells (Papagiannakis et al., 2018; Daniele et al., 2018) in patients with PD, demonstrating significant diagnostic accuracy of serum o - α -syn (sensitivity of 75% and specificity of 100%) (Williams et al., 2016). Higher levels of oligomeric α -syn (o - α -syn) and the o - α -syn/ t - α -syn ratio in the saliva of PD patients compared to controls have been reported (Devic et al., 2011; Al-Nimer et al., 2014; Vivacqua et al., 2016; Shaheen et al., 2020). A meta-analysis revealed that o - α -syn in saliva has the potential to become a diagnostic biomarker in PD (Bougea et al., 2019). However, results from some studies have shown decreased levels of o - α -syn in PD samples or no significant differences compared to healthy controls (Park et al., 2011; Yanamandra et al., 2011; Wang et al., 2015). Recently, a novel saliva biomarker panel composed of o - α -syn, t -tau, microtubule-associated protein light chain 3 beta (MAP-LC3 β), and tumor necrosis factor alpha (TNF- α) showed higher levels in *de novo* PD patients than in healthy controls (De Bartolo et al., 2023). The combined measurement of the ratios of o - α -syn/ t - α -syn and amyloid- β (A β -42)/total-tau improves the differentiation of PD from tauopathies (Meloni et al., 2023). PMCA-based evaluation of o - α -syn could differentiate MSA from PD/DLB patients (Rossi et al., 2020; Singer et al., 2020). There have been attempts to evaluate o - α -syn in erythrocytes as a potential biomarker in PD. Results from a recent large study showed that levels of o - α -syn in erythrocytes were higher in PD patients than in patients with MSA and healthy controls (Li et al., 2019). However, most recent studies have not confirmed o - α -syn as a biomarker for differentiating PD from other neurodegenerative disorders (Eusebi et al., 2017; Majbour et al., 2020; Luo et al., 2024).

Post-translational phosphorylation modifies α -syn, contributing to its misfolding and aggregation (Oueslati et al., 2010). The primary modified form of α -syn is phosphorylation at serine 129 (pS129- α -syn), which represents the main target in biomarker studies of phosphorylated forms of α -syn (p- α -syn) (Anderson et al., 2006). Most studies have reported elevated levels of CSF pS129- α -syn in PD compared to controls, although some studies did not reach statistical significance (Majbour et al., 2016; Oosterveld et al., 2020). Similar levels of CSF pS129- α -syn were observed in atypical parkinsonian syndromes, limiting



its use in differential diagnosis (van Steenoven et al., 2018; Foulds et al., 2012; Majbour et al., 2020). However, results from several studies have shown higher levels of CSF pS129- α -syn in PD compared to MSA patients, although this finding was not confirmed in other studies (Wang et al., 2012; Schulz et al., 2021; Foulds et al., 2012; Constatidines et al., 2021; Cao et al., 2020). Several reports have questioned the potential of this biomarker in differentiating PD from tauopathies, including PSP, CBS, and AD (Schulz et al., 2021; Foulds et al., 2012; Constatidines et al., 2021; van Steenoven et al., 2018; Swallow and Counsell, 2023). Results of a recent study reported lower levels of t- α -syn and higher levels of o- α -syn and p-tau in PD patients compared to healthy controls (Daniele et al., 2018). A promising diagnostic marker for PD may be the combination of different α -synforms, particularly an increased ratio of Ser-129-p- α -syn and/or o- α -syn to t- α -syn (Zheng et al., 2021; Parnetti et al., 2014; van Steenoven et al., 2018; Majbour et al., 2020; Stewart et al., 2015).

2.2 Disease progression and α -syn

Available data on CSF t- α -syn levels throughout the PD course show contradictory results, since α -syn is aggregated in Lewy bodies but also released from degenerating synapses (Majbour et al., 2016; Hall et al., 2026; Mollenhauer et al., 2019; Paoletti et al., 2020). Most studies suggest that t- α -syn measured in CSF, blood, and

EVs has a limited ability to predict and track PD progression (Mollenhauer et al., 2011; Eusebi et al., 2017; Wang et al., 2018; Stuendl et al., 2016; Shi et al., 2014; Niu et al., 2020; Jiang et al., 2020; Parnetti et al., 2019; Constatidines et al., 2021). CSF t- α -syn does not change over time in relation to motor or cognitive symptoms (Mollenhauer et al., 2017; Hall et al., 2026). However, a few studies have suggested that higher CSF t- α -syn correlates with greater PD progression as a manifestation of more pronounced neurodegeneration (Hall et al., 2015). Kang et al. observed a significant decrease in the o- α -syn/t- α -syn ratio in Hoehn and Yahr stage I (H&Y stage I) PD patients and a significant increase in the ratio in HY stage II-IV PD patients, suggesting a possible role as a biomarker of PD progression (Kang et al., 2016).

CSF o- α -syn levels increased at a 4-year follow-up in the PD group and correlated with motor progression (Majbour et al., 2021), particularly with postural instability and gait difficulties (Majbour et al., 2016). Despite some conflicting results, most studies suggest that CSF o- α -syn predicts PD progression (Russo et al., 2021; Majbour et al., 2016, 2021).

Results from a prospective study evaluating 122 PD patients and 68 controls, followed for 3 years, showed that plasma levels of t- α -syn and pS129- α -syn were significantly higher in PD patients than in controls, and pS129- α -syn levels were higher in patients with advanced motor symptoms. PD patients with a specific baseline pS129- α -syn level (> 8.5 fg/ml) experienced greater motor progression than those with lower pS129- α -syn levels (< 8.5

fg/ml, $p = 0.03$) (Lin et al., 2019a). Results from some other studies confirm the correlation of pS129- α -syn levels with the progression of motor symptoms (Stewart et al., 2015; Majbour et al., 2016). However, some studies have reported lower pS129- α -syn levels in later disease stages, possibly because of extensive neuronal damage (Majbour et al., 2021; Foulds et al., 2012).

3 Alzheimer's disease-related biomarkers

3.1 Differentiating Parkinson's disease from other disorders

Studies have shown that amyloid plaques and neurofibrillary tangles can coexist with α -syn pathology in PD (Jellinger K, 2008; Compta et al., 2011; Irwin et al., 2013; Jellinger et al., 2002; Williams et al., 2016). A combination of reduced A β -42 and increased total tau (t-tau) and phosphorylated tau (p-tau), known as an AD biomarker profile, can occur in synucleinopathies, including PD, in patients with cognitive decline (Kurata et al., 2007; Clinton et al., 2010). Current data show a low diagnostic value of CSF A β -42 in PD patients (Kang et al., 2013; Stav et al., 2015; Delgado-Alvarado et al., 2016; Kang et al., 2016). However, most studies demonstrate that lower CSF levels of A β -42 are related to worse cognitive function in PD patients (Irwin et al., 2020, 2017; Parnetti et al., 2014; Alves et al., 2014; Kang et al., 2013; Montine et al., 2010; Compta et al., 2013). Patients with dementia with Lewy bodies (DLB), AD, and PDD presented with lower levels of CSF A β -42 compared to PD patients without dementia (Vranová et al., 2014; Kaerst et al., 2013). In another study, the CSF AD-specific biomarker profile was found in a higher percentage of patients with DLB (25%) compared to only 3% of patients with PD (van Steenoven et al., 2016).

Studies evaluating t-tau and p-tau in CSF show contradictory results (Alves et al., 2014; Hu et al., 2017; Chiu et al., 2021). A recent study demonstrated higher serum p-tau levels in PD compared to healthy controls and in PD with cognitive impairment compared to PD without cognitive impairment (Blommer et al., 2023).

3.2 Predicting disease progression and phenotype

Decreased levels of A β -42 in combination with increased levels of t-tau and p-tau in CSF have been correlated with greater progression of cognitive decline in PD and AD (Berlyand et al., 2016; Leaver and Poston, 2015; Siderowf et al., 2010; Henderson et al., 2019). Available data show that PD patients with lower CSF A β -42 levels at disease onset have a more rapid progression to dementia (Parnetti et al., 2014; Siderowf et al., 2010; Alves et al., 2014), suggesting that this biomarker may serve as a prognostic factor for the development of cognitive impairment (Blennow et al., 2016). An AD-related biomarker profile in PD patients has been correlated with

faster progression to dementia, greater memory deficits, and the akinetic-rigid disease form (Irwin et al., 2017; Compta et al., 2011; Halliday et al., 2008; Howlett et al., 2015; Sabbagh et al., 2009; Coughlin et al., 2019). However, other studies failed to confirm more pronounced AD biomarkers in the diffuse-malignant subtype compared to the mild motor dominant subtype of PD (Fereshtehnejad et al., 2017, 2015). In a prospective study evaluating PD patients for 3 years, lower initial CSF A β -42 levels predicted cognitive and motor decline, autonomic dysfunction, and dopa-resistant gait impairments (Rochester et al., 2017). A few studies have demonstrated that p-tau181 levels could predict disease progression and cognitive decline (Batzu et al., 2022; Chiu et al., 2021; Pagonabarraga et al., 2022).

4 Neuroinflammation

In recent years, an increasing number of studies have evaluated various inflammatory mediators as potential biomarkers in PD, given the evidence that immune cells in the central nervous system (CNS) and peripheral blood are involved in PD pathogenesis (Ransohoff, 2016; Caldi Gomes et al., 2022; Nayak et al., 2015; Dixit et al., 2019; Magdalinou et al., 2017; Kouli and Williams-Gray, 2020). Microglia, which represent the primary innate immune cells of the CNS, can be activated by misfolded proteins and protein aggregates, thereby inducing neuroinflammation (de Araujo et al., 2021). Different proteins, including α -syn, act as epitopes that activate the immune response in peripheral blood mononuclear cells (PBMCs) in patients with PD (Sulzer et al., 2017; White et al., 2018). Inflammatory processes in PD appear to be most prominent in the early stages of the disease and may persist throughout disease progression (Lindestam Arlehamn et al., 2020).

Proteins released from astrocytes measured in blood have been evaluated in PD and other neurodegenerative disorders. Glial fibrillary acidic protein (GFAP) levels were elevated in PD patients compared to healthy controls, but this marker was unable to differentiate PD from atypical parkinsonian syndromes (Su et al., 2012; Oeckl et al., 2019). Chitinase-3-like protein 1 (YKL-40) and monocyte chemoattractant protein-1 (MCP-1) were significantly higher in tauopathies than in PD (Olsson et al., 2013; Wennstrom et al., 2015).

Results from studies evaluating inflammatory markers in blood have shown that IL-1 β and CRP, and to a lesser extent IL-2, IL-6, IL-8, IFN- γ , and TNF- α , may have diagnostic value in PD (Hu et al., 2015; Miliukhina et al., 2020; Rocha et al., 2018; Lian et al., 2019; Chatterjee et al., 2020; Fan et al., 2020; Schroder et al., 2018; Delgado-Alvarado et al., 2017; Miliukhina et al., 2020; Gupta et al., 2016; Calvani et al., 2020; Usenko et al., 2020; Eidson et al., 2017; Martin-Ruiz et al., 2020; Qiu et al., 2019). Elevated levels of CRP, IL-6, IL-10, TNF- α and chemokine (C-C motif) ligand 5 (CCL5) have also been reported in PD patients (Jin et al., 2020; Qiu et al., 2019; Vesely et al., 2018; Karpenko et al., 2018; Kim et al., 2018; Kouchaki et al., 2018). A few studies have evaluated CSF inflammatory markers, showing higher levels of IL-1 β in PD

patients compared to healthy controls (Hu et al., 2015; Chen et al., 2018; Iwaoka et al., 2020). Some studies have reported elevated CSF levels of IL-6 and IL-8 in PD patients, although these results were not consistently replicated in other studies (Chen et al., 2018; Iwaoka et al., 2020; Lian et al., 2019; Schroder et al., 2018; Hall et al., 2018; Hu et al., 2019; Santaella et al., 2020; Delgado-Alvarado et al., 2017). There are reports that higher blood levels of IL-10 are associated with greater motor and cognitive impairment (Usenko et al., 2020; Martin-Ruiz et al., 2020). Other studies have shown that higher blood levels of IL-1 β , IL-15, IFN- γ , S100B, TNF- α , and VCAM1, together with lower levels of anti-inflammatory cytokines IL-4 and IL-12p40, are associated with worse motor function in PD patients (Eidson et al., 2017; Fan et al., 2020; Lerche et al., 2022; Perner et al., 2019; Yilmaz et al., 2018). A few longitudinal studies have reported higher blood levels of CRP, C3, and C4 in PD patients with cognitive decline (Mollenhauer et al., 2019; Vesely et al., 2019). Several cross-sectional studies have demonstrated that higher CSF levels of CRP, IL-6, MCP-1, FABP, IL-8, and YKL-40 are associated with worse cognitive function, and that higher levels of CRP and MCP-1 are associated with depression and fatigue in PD patients (Hall et al., 2018; Sanjari Moghaddam et al., 2018; Lindqvist et al., 2013).

However, variability in patient cohorts, differences in diagnostic methods, and gender-related differences in immune responses contribute to the inconsistent findings across studies evaluating different immune parameters in PD.

5 Extracellular vesicles

Extracellular vesicles (EVs), small particles released from many cell types, have been investigated as potential biomarkers for diagnosing different neurodegenerative disorders, including PD (Quek and Hill, 2017; Latifkar et al., 2019; Boing et al., 2014). They are composed of exosomes (50–150 nm), microvesicles (100–1000 nm), and apoptotic bodies (up to 5 μ m) (Agliardi et al., 2021). Different exosomal proteins, such as α -syn, inflammation-related markers, AD-related markers, and microRNA (miRNA), have been investigated as potential biomarkers for PD (Keighron et al., 2023; Hook et al., 2023; Margis et al., 2011).

5.1 Pathological proteins in exosomes

Neuron-derived extracellular vesicles (NDEVs) containing α -syn can cross the blood-brain barrier and can therefore be detected in peripheral fluids (Shi et al., 2014; Ishiguro et al., 2024). Results from a recently published meta-analysis showed a significant increase in α -syn levels detected in both total exosomes and neuron-derived exosomes from patients with PD compared with healthy controls (Kim et al., 2024). Another meta-analysis by Xylaki and colleagues confirmed that the detection of α -syn could serve as a potential biomarker for diagnosing PD (Xylaki et al., 2023). Reported data suggest that

measurement of t- α -syn in EVs from different biological fluids, including CSF, plasma/serum, or saliva, can distinguish PD from healthy controls (Stuendl et al., 2016, 2021; Zhao et al., 2019; Jiang et al., 2020; Niu et al., 2020; Dutta et al., 2021; Fu et al., 2020; Cao et al., 2019; Si et al., 2019; Zhao and Yang, 2021; Ohmichi et al., 2019; Xylaki et al., 2023; Church et al., 2024). There were no significant differences in pS129- α -syn in EVs compared with its levels in whole plasma in patients with PD. However, recent studies have reported that levels of pS129- α -syn in the cytosolic fraction of erythrocytes are significantly higher in PD patients than in controls (Tian et al., 2019; Foulds et al., 2012), even in the earliest stages of the disease (Li P. Y. et al., 2021). Another study did not confirm these findings (Chatterjee et al., 2020).

Studies performed on other biological fluids have shown elevated EV levels of p-Ser-1292 LRRK2 in urine from patients with PD (Wang et al., 2017; Fraser et al., 2016). Rani et al. (2019) confirmed higher neuronal EV α -syn levels in saliva, suggesting its potential as a PD biomarker. Recent results from a longitudinal study demonstrate an increase in both t- α -Syn and o- α -Syn in PD-derived salivary EVs compared to healthy controls, with higher levels observed in patients with cognitive decline and motor fluctuations. There were no correlations with H&Y stage, and no change in α -syn levels after 1 year of follow-up (Gurgone et al., 2026). Cao et al. evaluated different forms of α -syn in saliva EVs in PD patients, showing increased levels of o- α -syn and o- α -syn/t- α -syn ratios with no significant differences in p- α -syn and p- α -syn/t- α -syn ratios compared to healthy controls (Cao et al., 2019). The results from another study, using Nanoparticle Tracking Analysis (NTA), revealed a higher concentration of the fluorescence-dye-labeled salivary EVs in PD compared to controls ($p = 0.0001$) with higher levels of t- α -syn, p- α -syn/t- α -syn ratios in PD patients, and a significant increase in t- α -syn in prodromal PD patients (Rastogi et al., 2023).

Although EVs offer a window into CNS-derived cargo, several methodological challenges limit their current clinical utility. Variability in isolation methods (ultracentrifugation vs. precipitation vs. immunocapture), differences in EV subtypes enriched (LICAM-based vs. non-enriched neuronal EVs), and pre-analytical factors (processing time, temperature, hemolysis) can drastically alter measured α -syn levels in EVs. Saliva EVs deserve particular scrutiny: several studies report altered α -syn species in salivary EVs, but results are not uniformly replicated across cohorts. The study of Gurgone et al. provides important insights but also highlights the need for standardization and multi-cohort validation (Gurgone et al., 2026). Interpretation should be cautious: elevated EV-associated α -syn in saliva/plasma may reflect peripheral release, BBB/transporter dynamics, or peripheral mimicry of CNS pathology. Therefore, claims of disease specificity require replication in independent samples and cross-validation with CSF and neuroimaging data. A critical objective going forward is to establish consensus protocols for EV isolation from plasma, CSF, and saliva. EV isolation protocols from plasma are more extensively studied, with several established methods such as ultracentrifugation, size exclusion chromatography, and precipitation-based approaches available. However, a universally

accepted protocol for purifying plasma-derived EVs is still lacking, as none of the aforementioned methods is considered the “gold standard” (Takov et al., 2018; Veerman et al., 2021; Welsh et al., 2024; Zanganeh et al., 2026). In contrast, while salivary EV isolation and analysis methods are still under development, there is progress in methodological comparisons being published, and the latest version of MISEV guidelines (MISEV2023) includes a dedicated section on saliva (Welsh et al., 2024).

There is also a need to integrate RT-QuIC/PMCA findings with EV cargo data to determine whether EV-associated seeds correlate with seeding activity in the same samples, potentially strengthening diagnostic specificity.

Measurement of α -syn levels in NDEVs may contribute to better differentiation of PD from other atypical parkinsonian syndromes, especially when combined with levels of other proteins such as clusterin (Jiang et al., 2020; Dutta et al., 2021; Jiang et al., 2021). Evidence from recent studies suggests that α -syn derived from NDEVs in blood may even predict the development of PD in patients at risk, including those with symptoms of RBD, hyposmia, or non-manifesting carriers of *GBA* mutations (Yan et al., 2024).

Regarding other proteins, plasma EV levels of tau and A β -42 have been found to be significantly increased in PD patients compared with healthy controls, particularly in relation to cognitive impairment (Chan et al., 2023; Parnetti et al., 2019). Elevated levels of A β -42 and tau, together with increased α -syn and lower levels of serine-phosphorylated insulin receptor substrate (IRS-p312) in serum EVs, predict worse motor and cognitive progression in PD patients (Chung et al., 2021; Chan et al., 2023; Blommer et al., 2023). Plasma exosomal tau may differentiate PD from healthy controls but not from AD (Shi et al., 2016). Among chemokines in extracellular fluids that regulate inflammation and immune responses, C-X-C motif chemokine ligand 12 (CXCL12) in plasma exosomes has been proposed as a potential biomarker for diagnosing PD (Bagheri et al., 2018; Li et al., 2022). Results from another study revealed that CXCL12 levels correlated with autonomic dysfunction, while α -syn levels in NDEVs correlated with clinical stage as well as motor and non-motor symptoms in PD (Jiang et al., 2020).

However, technical challenges, including inadequate controls for the isolation of neuronal extracellular vesicles and variability in α -syn forms, contribute to the lack of protocol standardization and limit their applicability in clinical practice (Bernhardt et al., 2024; Kluge et al., 2024; Norman et al., 2021).

Based on these studies, it can be concluded that the field of saliva EV biomarkers is promising and rapidly evolving, with methodological comparisons being published and the latest version of the MISEV guidelines (MISEV2023), including a dedicated section on saliva (Welsh et al., 2024). Future research is warranted to characterize the cargo of salivary EVs, to determine their potential for early diagnosis and disease monitoring, and to explicitly report normalization strategies and quality controls to improve comparability. Moreover, where α -syn within EVs is detected, parallel RT-QuIC testing of the same biofluid can help determine whether EV cargo reflects seed-competent species. This integration has the potential to improve diagnostic specificity for PD vs. atypical parkinsonian disorders. Finally, it is also of high clinical relevance to emphasize that the

strongest translational signal currently comes from multi-modal panels (EV cargo + inflammatory markers + AD biomarkers) rather than single analytes. To establish clinical utility, the field should therefore prioritize multi-marker, cross-fluid validation in longitudinal cohorts.

5.2 MicroRNA in exosomes

MicroRNAs are small non-coding RNAs with 20–22 nucleotides that play a role in the pathogenesis of different neurodegenerative disorders, including PD (Maiese, 2022; Guévremont et al., 2023; van Wamelen et al., 2020). Available data suggest that certain microRNAs in plasma exosomes, including miR-24, miR-23b-3p, miR-29c, miR-195-3p, and miR-331-5p, have potential as biomarkers for PD (Harischandra et al., 2018). Among microRNAs, miR-30c and miR-148b were reported to be specific to PD, while miR-24, miR-34b, and miR-148b were more prevalent in MSA compared to PD (Villar-Menéndez et al., 2014; Valletlunga et al., 2014). In another study, downregulation of miR-19b and upregulation of miR-195 and miR-24 demonstrated accuracy ranging from 70 to 90% in differentiating PD from healthy controls. Several studies evaluating different microRNAs in saliva have shown variable results. Results from the recent study show decreased levels of miR-153 and miR-223 in the saliva of PD patients, with no correlation with H&Y stage (Cressatti et al., 2020). In another study, miR-29a-3p and miR-29c-3p were decreased, while miR6765-5p was increased in PD patients, with further results showing the potential of miR-29 to differentiate PD from healthy controls, and miR-29a-3p PD from essential tremor (ET) and multiple system atrophy (MSA) (Jiang et al., 2020). Evaluation of miRNA in plasma EVs revealed upregulation of miR-151a-5a, let-7e-5p, miR-9-5p, miR-127-3p, and miR-146a-5p, and downregulation of miR-93-5p (Nie et al., 2020; Sproviero et al., 2021; Li et al., 2024) in PD patients. Results from another study evaluating miRNA in serum EVs showed decreased levels of let-7i-5p, miR-18a-5p, and miR-20a-5p, and increased levels of miR-143-3p, miR-151a-3p, and miR-151a-5p in PD (Miyamoto et al., 2022).

From the results of the aforementioned studies, it can be concluded that microRNAs in NDEVs offer complementary information to protein cargo and may reflect CNS-derived regulatory networks. However, normalization, platform choice (qRT-PCR vs. sequencing), and hemolysis remain major sources of variability that hinder cross-cohort replication. Thus, while key miRNA candidates show promise in certain cohorts, external validation is needed. Once external validation experiments are completed (including the usage of synthetic spike-ins, exogenous controls, and assessment of the impact of hemolysis on plasma/serum miRNA profiles), multi-omic EV signatures combining miRNA and protein cargo, anchored by robust normalization and cross-platform harmonization, would strengthen translational potential. Table 1 provides an integrated view of the diagnostic and prognostic strength across major biomarker classes in PD biofluids; Table 2 compares biomarkers across fluids, and Table 3 lists saliva EV studies.

TABLE 1 A cross-class synthesis of major biomarkers in PD biofluid analysis.

Biomarker class	Representative biomarkers	Fluids (compartments)	Evidence type	Study designs	Strength of evidence	Key references	Notes
α -syn species	total α -syn (t- α -syn); oligomeric α -syn (o- α -syn); phosphorylated α -syn (pS129- α -syn)	CSF; plasma/serum; saliva	Observational studies; secondary analyses; some SAA data	Cross-sectional; longitudinal	Low - High	Majbour et al., 2016; Rossi et al., 2020; Siderowf et al., 2023; van Steenoven et al., 2018	Results should be interpreted cautiously due to assay/cohort heterogeneity
SAA/RT-QuIC (seed amplification)	α -syn seed amplification assays (RT-QuIC; PMCA)	CSF; serum/plasma; saliva	Diagnostic assay data; prodromal signals	Cross-sectional; some longitudinal	High	Rossi et al., 2020; Siderowf et al., 2023; Okuzumi et al., 2023; Poggiolini et al., 2022	Requires standardization and broader validation
Neurofilament light chain (NfL)	NfL in CSF and blood	CSF; plasma/serum	Diagnostic and prognostic biomarker data	Cross-sectional; longitudinal	Moderate—High	Bridel et al., 2019; Lin et al., 2019a; Ma et al., 2021	Confounded by age and comorbidities; best in panels
Glial fibrillary acidic protein (GFAP)	GFAP in serum/plasma	Blood	Prognostic biomarker data	Cross-sectional; longitudinal	Moderate	Su et al., 2012; Lin et al., 2023; Tang et al., 2023	More informative when combined with other markers
YKL-40	YKL-40 in CSF	CSF	Differential biomarker data across neurodegenerative disorders	Cross-sectional	Moderate	Wennstrom et al., 2015; Hall et al., 2018	Not PD-specific; more informative for differential diagnosis
AD biomarkers	(A β 42, total-tau [t-tau], phospho-tau [p-tau])	CSF; blood	Differential diagnosis; PD with cognitive impairment	Cross-sectional; longitudinal	Moderate	Irwin et al., 2017; Rochester et al., 2017; Halliday et al., 2008	Useful for risk stratification in relation to cognitive changes in PD
Exosomal miRNAs	miR-24; miR-29c; miR-195; mir-331-5p; others	Plasma exosomes; saliva exosomes	Diagnostic/prognostic signals	Cross-sectional; longitudinal	Low-Moderate	Margis et al., 2011; Villar-Menéndez et al., 2014; Guévremont et al., 2023	High methodological variability; replication needed
EV cargo in NDEVs (α -syn, tau, A β ; miRNA)	α -syn in NDEVs; tau/A β cargo; exosomal miRNA	Plasma exosomes; CSF exosomes	Diagnostic/prognostic	Cross-sectional; longitudinal	Moderate	Shi et al., 2014; Jiang et al., 2020; Chan et al., 2023	Promising but requires standardization

TABLE 2 PD biomarkers: cross-fluid performance.

Biomarker	Fluid(s) tested	Study designs (cross-sectional/ longitudinal)	Prognostic/ progression data	Population/ comparison groups	Key references	Notes
α -syn SAA/RT-QuIC	CSF; plasma/serum; saliva	Cross-sectional; longitudinal	Progression associations	PD vs controls; PD vs DLB/MSA; prodromal groups	Rossi et al., 2020; Siderowf et al., 2023; Okuzumi et al., 2023; Poggiolini et al., 2022	Assay subtypes may differ as well as sample handling
Total α -syn (t- α -syn)	CSF; plasma	Cross-sectional; longitudinal	Progression associations	PD vs. controls; PD subtypes	Førland et al., 2020; Foulds et al., 2012; Mollenhauer et al., 2011	Highly assay- and cohort-dependent
Neurofilament light chain (NFL)	CSF; plasma/serum	Cross-sectional; longitudinal	Cognitive/motor progression	PD vs MSA/PSP	Bridel et al., 2019; Lin et al., 2019a; Ma et al., 2021	Age-adjusted analyses recommended
Glial fibrillary acidic protein (GFAP)	Serum/plasma	Cross-sectional; longitudinal	Cognitive progression signals	PD vs controls; conversion risk	Lin et al., 2023; Tang et al., 2023	Best in combination panels
YKL-40	CSF	Cross-sectional	Cognitive associations	PD vs. AD/tauopathies	Wennstrom et al., 2015; Hall et al., 2018	More informative for differential diagnosis
AD biomarkers (A β 42, t-tau, p-tau)	CSF; serum	Cross-sectional; longitudinal	Cognitive impairment	PD with cognitive impairment (PDD); dementia risk	Irwin et al., 2017; Rochester et al., 2017	Useful for risk stratification in cognitive changes in PD
Exosomal miRNAs	Plasma exosomes; saliva exosomes	Cross-sectional; longitudinal	Cognitive/clinical correlations	PD vs. controls; MSA	Margis et al., 2011; Villar-Menéndez et al., 2014; Guévremont et al., 2023	High methodological variability; replication needed
EV cargo in NDEVs (α -syn, tau, A β ; miRNA)	Plasma exosomes; CSF exosomes	Cross-sectional; longitudinal	Cognition, progression signals	PD vs controls; prodromal risk	Shi et al., 2014; Jiang et al., 2020; Chan et al., 2023	Promising but requires harmonized protocols

TABLE 3 Saliva EV studies.

Study (Author, Year)	Saliva EV cargo studies	Isolation method	Population/ comparison groups	Key findings	Limitations
Cao et al. (2019)	α-syn (t-/o- forms) in salivary EVs	Salivary EV isolation with differential centrifugation and affinity capture	PD vs controls	Elevated salivary EV α-syn	Small cohorts; heterogeneity in methods
Rani et al. (2019)	Neuronal exosomal α-synuclein in saliva	Neuronal marker-based enrichment in saliva EVs	PD vs. controls	Higher neuronal EV α-syn	Pilot study; replication needed
De Bartolo et al. (2023)	Salivary biomarker panel (contextual, not strictly EV)	Saliva collection; multi-omics readouts	Panel differentiates <i>de novo</i> PD from controls in initial cohorts	Integration with EV data not direct	Not strictly EV-focused
Gurgone et al. (2026)	α-syn (t-/o- forms) in salivary EVs in longitudinal study	Salivary EV isolation with differential centrifugation	PD vs controls	Elevated salivary EV α-syn; higher o-α-syn levels in cognitive decline and motor fluctuations; no change in 1-year follow-up	Small cohorts; short follow-up
Rastogi et al. (2023)	α-syn (t-/p- forms), CD9, CD63, flotillin-1, L1CAM in salivary EVs	Salivary EV isolation with differential centrifugation and ultrafiltration	PD vs controls	Elevated salivary EV t-α-syn; p-α-syn, p/t-α-syn ratio, CD9, CD63, flotillin-1, L1CAM; elevated t-α-syn in prodromal PD stage	Small cohorts

6 Non-specific biomarkers of neurodegeneration

6.1 Neurofilament light chain

Neurofilament light chain (NfL) is a protein released into CSF and blood following neuro-axonal damage and neurodegeneration (Khalil et al., 2024). Most studies have failed to provide evidence supporting NfL as a biomarker for differentiating PD from healthy controls, which could be attributed to confounding factors, including age, body mass index (BMI), and cardiovascular risks (85-89). Some studies have reported significantly higher serum NfL levels in PD patients than in patients with essential tremor (ET) and healthy controls (Liu et al., 2023; Hansson et al., 2017).

However, NfL shows potential as a biomarker for differentiating PD from atypical parkinsonian disorders. Higher CSF NfL levels have been reported in different atypical parkinsonian disorders, with excellent accuracy in distinguishing PD from PSP (sensitivity 93%, specificity 95%), MSA (sensitivity 89%, specificity 93%), and CBS (sensitivity 100%, specificity 93%) (Hansson et al., 2017; Herbert et al., 2015; Bridel et al., 2019).

Results from different studies have shown conflicting data regarding the association between NfL levels and motor symptoms in PD (Niemman et al., 2021; Oosterveld et al., 2020; Pötter-Nerger et al., 2022). Lin et al. (2019b) evaluated plasma NfL levels and cognitive symptoms in 116 PD patients, 22 patients with MSA, and 40 healthy controls at baseline and after 3 years. Plasma NfL levels were significantly higher in MSA patients than

in PD patients and controls, and higher in PD patients with more pronounced motor symptoms and dementia. Additionally, higher baseline NfL levels correlated with greater motor and cognitive progression. Other studies have also reported greater cognitive progression in PD patients with higher NfL levels measured in CSF or blood (Oosterveld et al., 2020; Ma et al., 2021; Lin et al., 2019a). These findings suggest that NfL may serve as a biomarker for distinguishing PD from atypical parkinsonian disorders and for predicting cognitive decline.

6.2 Glial fibrillary acidic protein

In CNS damage, astrocytes release the intermediate filament protein glial fibrillary acidic protein (GFAP), which can be measured in CSF and blood (Ishiki et al., 2016), (Liddelow and Barres, 2017). GFAP is not disease-specific, as its levels are increased in different disorders, including traumatic brain injury, cerebrovascular disorders, and neurodegenerative diseases (Lotankar et al., 2017). Serum GFAP levels have been reported to be higher in PD patients compared with healthy controls, with no significant difference observed between PD patients and those with acute stroke (Su et al., 2012). Results from recent studies have shown that baseline plasma GFAP levels may predict rapid progression to cognitive decline and postural instability (Lin et al., 2023; Liu et al., 2023; Lin et al., 2023; Tang et al., 2023). Results from other studies also suggest that GFAP may serve as a biomarker of

progression to dementia in PD, showing higher levels in PDD compared with PD MCI and healthy controls (Bartl et al., 2023; Tang et al., 2023; Lin et al., 2023; Che et al., 2024). Other studies suggest that a combination of GFAP and neurofilament light chain (NfL) can differentiate PDD from PD without dementia (Mao et al., 2023) and correlates with the progression of motor symptoms (Youssef et al., 2023). Based on the available data, GFAP has potential as a biomarker of disease progression, but not as a diagnostic biomarker for differentiating PD from other conditions.

In summary, higher NfL levels track progressive neurodegeneration and cognitive decline across PD and related disorders, although specificity for PD remains a challenge in the absence of a PD-specific biomarker panel, GFAP and other glial markers may predict conversion to dementia and correlate with motor progression in longitudinal cohorts, while CSF A β 42, total tau (t-tau), and phosphorylated tau (p-tau) are associated with faster cognitive decline and may identify patients at higher risk for PD dementia (PDD). On translational relevance, the biomarkers should always be evaluated for which ones demonstrate the most consistent associations with Hoehn–Yahr stages, UPDRS scores, and cognitive scales (MoCA, MMSE), and whether they can predict response to dopaminergic therapy or progression to dementia, highlighting the critical need for longitudinal, treatment-stratified cohorts to establish clinical utility and inform trial design.

7 Conclusion

This review summarizes current data on various biofluid biomarkers for PD, including α -syn variants, different proteins or microRNAs released from EVs, and markers associated with neuroinflammation and AD. While significant progress has been made in identifying potential biomarkers in various biofluids, including plasma, CSF, and saliva through advances in the detection of pathological α -syn using PMCA and RT-QuIC assays, which have provided new opportunities for the diagnosis of PD and its differentiation from other neurodegenerative disorders, the translation of these findings into clinical practice is hindered by several major challenges. These challenges include the lack of standardized methodologies for sample collection, processing, and analysis, as well as the need for longitudinal studies to assess the predictive and prognostic value of candidate biomarkers. Additionally, variability among studies, including differences in patient populations with respect to different stages and PD subtypes, the limited inclusion of patients with atypical parkinsonian syndromes, and technical issues such as sample contamination, have further limited the clinical applicability of these biomarkers.

Recent studies highlight the potential of NDEVs containing t- α -syn, pS129- α -syn, A β 42, chemokines, and microRNAs as biomarkers for PD diagnosis, disease progression, and prediction of future disease development. The CSF AD biomarker profile has been associated with worse cognitive function in PD patients

and may serve as a prognostic factor for the development of dementia. In contrast, markers of neuroinflammation have generally failed to demonstrate applicability for detecting or monitoring PD.

Salivary EVs, in particular, represent a promising, but still largely unexplored, source of biomarkers for PD. Further research is warranted to characterize the cargo of salivary EVs and to determine their potential for early diagnosis and disease monitoring. Integrating EV-based biomarkers with other diagnostic tools, such as RT-QuIC, may improve the accuracy and reliability of PD diagnosis.

Future research should prioritize large-scale, multi-center studies that incorporate standardized protocols and longitudinal follow-up with special emphasis on a multi-marker panel approach. These studies should also focus on correlating biomarker levels with clinical features of the disease, such as disease stage, motor and non-motor symptoms and response to treatment. Ultimately, the development of validated biomarkers will enable earlier and more accurate diagnosis, facilitate personalized treatment strategies, and improve the lives of individuals affected by PD.

Author contributions

PB: Conceptualization, Data curation, Investigation, Writing – original draft. GŠ: Conceptualization, Funding acquisition, Resources, Supervision, Validation, Visualization, Writing – review & editing.

Funding

The author(s) declared that financial support was received for this work and/or its publication. This work was funded by the European Commission through the National Recovery and Resilience Plan, under the programme Targeted Scientific Research G.A. NPOO.C3.2.R3-I1.04.0257, Detection and validation of molecular markers of inflammation in Alzheimer's and Parkinson's disease, multiple sclerosis, and schizophrenia (4BrainFlames) and by institutional NPOO grant from the University of Zagreb no. 10106-25-2986, Functional inflammatory response evaluation in Alzheimer's and Parkinson's disease, multiple sclerosis, and schizophrenia (FIRE4).

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

References

- Abdi, I. Y., Majbour, N. K., Willemse, E. A. J., van de Berg, W. D. J., Mollenhauer, B., Teunissen, C. E., et al. (2021). Preanalytical stability of CSF total and oligomeric alpha-synuclein. *Front. Aging Neurosci.* 3:85. doi: 10.3389/fnagi.2021.638718
- Agliardi, C., Meloni, M., Guerini, F. R., Zanzottera, M., Bolognesi, E., Baglio, F., et al. (2021). Oligomeric α -Syn and SNARE complex proteins in peripheral extracellular vesicles of neural origin are biomarkers for Parkinson's disease. *Neurobiol. Dis.* 148:105185. doi: 10.1016/j.nbd.2020.105185
- Al-Nimer, M. S. M., Mshatat, S., and Abdulla, H. I. (2014). Saliva α -synuclein and a high extinction coefficient protein: a novel approach in assessment biomarkers of Parkinson's disease. *N. Am. J. Med. Sci.* 6, 633–637. doi: 10.4103/1947-2714.147980
- Alves, G., Lange, J., Blennow, K., Zetterberg, H., Andreasson, U., Förlund M. G., et al. (2014). CSF A β 42 predicts early-onset dementia in Parkinson disease. *Neurology* 82, 1784–1790. doi: 10.1212/WNL.0000000000000425
- Anderson, J. P., Walker, D. E., Goldstein, J. M., Banducci, K., Caccavello, R. J., Barbour, R., et al. (2006). Phosphorylation of Ser-129 is the dominant pathological modification of alpha-synuclein in familial and sporadic Lewy body disease. *J. Biol. Chem.* 281, 29739–29752. doi: 10.1074/jbc.M600933200
- Bagheri, V., Khorramdelazad, H., Hassanshahi, G., Moghadam-Ahmadi, A., and Vakilian, A. (2018). CXCL12 and CXCR4 in the peripheral blood of patients with Parkinson's disease. *Neuroimmunomodulation* 25, 201–205. doi: 10.1159/000494435
- Bartl, M., Dakna, M., Schade, S., Otte, B., Wicke, T., Lang, E., et al. (2023). Blood markers of inflammation, neurodegeneration, and cardiovascular risk in early Parkinson's disease. *Mov. Disord.* 38, 68–81. doi: 10.1002/mds.29257
- Batzu, L., Rota, S., Hye, A., Zetterberg, H., Blennow, K., and Aarsland, D. (2022). Plasma p-tau181, neurofilament light chain and association with cognition in Parkinson's disease. *NPJ Parkinsons Dis.* 8:154. doi: 10.1038/s41531-022-00384-x
- Bellomo, G., De Luca, C. M. G., Paoletti, F. P., Gaetani, L., Moda, F., and Parnetti, L. (2022). alpha-Synuclein seed amplification assays for diagnosing synucleinopathies: the way forward. *Neurology* 99, 195–205. doi: 10.1212/WNL.000000000000200878
- Berlyand, Y., Weintraub, D., Xie, S. X., Mellis, I. A., Rick, J., McKinsty, R. C., et al. (2016). An Alzheimer's disease-derived biomarker signature identifies Parkinson's disease patients with dementia. *PLoS One* 11:e0147319. doi: 10.1371/journal.pone.0147319
- Bernhardt, A. M., Nemati, M., Boros, F. A., Tóth, E. A., Pál, G., Molnár, K., Sántha, M., et al. (2024). α -synuclein seed amplification assays from blood-based extracellular vesicles in Parkinson's disease: an evaluation of the evidence. *Mov. Disord.* 39, 1269–1271. doi: 10.1002/mds.29923
- Biomarkers Definitions Working Group, (2001). Biomarkers and surrogate endpoints: Preferred definitions and conceptual frame work. *Clin. Pharmacol. Ther.* 69, 89–95. doi: 10.1067/mcp.2001.113989
- Blennow, K., Biscetti, L., Eusebi, P., and Parnetti, L. (2016). Cerebrospinal fluid biomarkers in Alzheimer's and Parkinson's diseases-from pathophysiology to clinical practice. *Mov. Disord.* 31:836–847. doi: 10.1002/mds.26656
- Blommer, J., Pitcher, T., Mustapic, M., Tran, J., Hsieh, C. H., Coffey, C. S., et al. (2023). Extracellular vesicle biomarkers for cognitive impairment in Parkinson's disease. *Brain* 146, 195–208. doi: 10.1093/brain/awac258
- Boing, A. N., van der Pol, E., Grootemaat, A. E., Coumans, F. A., Sturk, A., and Nieuwland, R. (2014). Single-step isolation of extracellular vesicles by size-exclusion chromatography. *J. Extracell. Vesicles* 3:23430. doi: 10.3402/jev.v3.23430
- Bougea, A., Koros, C., and Stefanis, L. (2019). Salivary alpha-synuclein as a biomarker for Parkinson's disease: a systematic review. *J. Neural Transm.* 126,1373–1382. doi: 10.1007/s00702-019-02062-4
- Bridel, C., van Wieringen, W. N., Zetterberg, H., Tijms, B. M., Teunissen, C. E., Alvarez-Cermeño, J. C., et al. (2019). Diagnostic value of cerebrospinal fluid neurofilament light protein in neurology: a systematic review and meta-analysis. *JAMA Neurol.* 76, 1035–1048. doi: 10.1001/jamaneurol.2019.1534

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

- Brockmann, K., Quadalti, C., Lerche, S., Rossi, M., Wurster, I., Baiardi, S., et al. (2021). Association between CSF alpha-synuclein seeding activity and genetic status in Parkinson's disease and dementia with Lewy bodies. *Acta Neuropathol. Commun.* 9:175. doi: 10.1186/s40478-021-01276-6
- Caldi Gomes, L., Galhoz, A., Jain, G., Roser, A. E., Maass, F., Carboni, E., et al. (2022). Multi-omic landscape scoping of human midbrains identifies disease-relevant molecular targets and pathways in advanced-stage Parkinson's disease. *Clin. Transl. Med.* 12:e692. doi: 10.1002/ctm2.692
- Calvani, R., Picca, A., Landi, G., Marini, F., Biancolillo, A., Coelho-Junior, H. J., et al. (2020). A novel multi-marker discovery approach identifies new serum biomarkers for Parkinson's disease in older people: anEXosomesinParkinson disease(EXPAND)ancillary study. *Geroscience* 42, 1323–1334. doi: 10.1007/s11357-020-00192-2
- Canaslan, S., Schmitz, M., Maass, F., Hermann, P., Da Silva Correia, S., et al. (2026). Detection of alpha-synuclein seeding activity in tear fluid in patients with Parkinson's disease. *NPJ Parkinsons Dis.* 12:41708653. doi: 10.1101/2025.01.16.633314
- Cao, Z., Wu, Y., Liu, G., Jiang, Y., Wang, X., Wang, Z., et al. (2019). Alpha-synuclein in salivary extracellular vesicles as a potential biomarker of Parkinson's disease. *Neurosci. Lett.* 696, 114–120. doi: 10.1016/j.neulet.2018.12.030
- Cao, Z., Wu, Y., Liu, G., Jiang, Y., Wang, X., Wang, Z. et al. (2020). Differential diagnosis of multiple system atrophy-parkinsonism and Parkinson's disease using alpha synuclein and external anal sphincter electromyography. *Front Neurol.* 11:1043. doi: 10.3389/fneur.2020.01043
- Cariulo, C., Martufi, P., Verani, M., Azzollini, L., Bruni, G., Weiss, A., Deguire, S. M., et al. (2019). Phospho-S129 alpha-synuclein is present in human plasma but not in cerebrospinal fluid as determined by an ultrasensitive immunoassay. *Front. Neurosci.* 13:889. doi: 10.3389/fnins.2019.00889
- Chahine, L. M., Beach, T. G., Brumm, M. C., Adler, C. H., Coffey, C. S., Mosovsky, S., et al. (2020). *In vivo* distribution of alpha-synuclein in multiple tissues and biofluids in Parkinson disease. *Neurology* 95, e1267–e1284. doi: 10.1212/WNL.00000000000010404
- Chan, L., Chung, C. C., Hsieh, Y. C., Wu, R. M., and Hong, C. T. (2023). Plasma extracellular vesicle tau, beta-amyloid, and alpha-synuclein and the progression of Parkinson's disease: a follow-up study. *Ther. Adv. Neurol. Disord.* 16:17562864221150329. doi: 10.1177/17562864221150329
- Chang, C.-W., Yang, S.-Y., Yang, C.-C., Chang, C.-W., and Wu, Y.-R. (2020). Plasma and serum alpha-synuclein as a biomarker of diagnosis in patients With Parkinson's Disease. *Front. Neurol.* 10:1388. doi: 10.3389/fneur.2019.01388
- Chatterjee, K., Roy, A., Banerjee, R., Choudhury, S., and Mondal, B., Halder, S., et al. (2020). Inflammation and alpha-synuclein in Parkinson's disease: a cross-sectional study. *J. Neuroimmunol.* 338:577089. doi: 10.1016/j.jneuroim.2019.577089
- Che, N., Ou, R., Li, C., Hou, Y., Wei, Q., Cao, B., et al. (2024). Plasma GFAP as a prognostic biomarker of motor subtype in early Parkinson's disease. *NPJ Parkinsons Dis.* 10:48. doi: 10.1038/s41531-024-00664-8
- Chen, X., Hu, Y., Cao, Z., Liu, Q., and Cheng, Y. (2018). Cerebrospinal fluid inflammatory cytokine aberrations in Alzheimer's disease, parkinson's disease, and amyotrophic lateral sclerosis: a systematic review and meta-analysis. *Front. Immunol.* 9:2122. doi: 10.3389/fimmu.2018.02122
- Chiu, M. J., Yang, S. Y., Chen, T. F., Chieh, J. J., Huang, T. Z., Yip, P. K., et al. (2021). Synergistic association between plasma A β (1–42) and p-tau in Alzheimer's disease but not in Parkinson's disease or frontotemporal dementia. *ACS Chem. Neurosci.* 12,1376–1383. doi: 10.1021/acscchemneuro.1c00010
- Chung, C. C., Chan, L., Chen, J. H., Bamodu, O. A., Chiu, H. W., and Hong, C. T. (2021). Plasma extracellular vesicles tau and β -amyloid as biomarkers of cognitive dysfunction of Parkinson's disease. *FASEB J.* 35:e21895. doi: 10.1096/fj.202100787R
- Church, M., Chen-Plotkin, A. S., and Walt, D. R. (2024). Measurement of alpha-synuclein as protein cargo in plasma extracellular vesicles. *Proc. Natl. Acad. Sci. USA* 121:e2408949121. doi: 10.1073/pnas.2408949121

- Clinton, L. K., Blurton-Jones, M., Myczek, K., Trojanowski, J. Q., and LaFerla, F. M. (2010). Synergistic interactions between abeta, tau, and alpha-synuclein: Acceleration of neuropathology and cognitive decline. *J. Neurosci.* 30, 7281–7289. doi: 10.1523/JNEUROSCI.0490-10.2010
- Compta, Y., Parkkinen, L., O'Sullivan, S. S., Vandrovicova, J., Holton, J. L., Collins, C., et al. (2011). Lewy- and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important? *Brain* 134, 1493–1505. doi: 10.1093/brain/awr031
- Compta, Y., Pereira, J. B., Rios, J., Ibarretxe-Bilbao, N., Junque, C., Bargallo, N., et al. (2013). Combined dementia-risk biomarkers in Parkinson's disease: a prospective longitudinal study. *Parkinsonism Relat. Disord.* 19, 717–724. doi: 10.1016/j.parkreldis.2013.03.009
- Concha-Marambio, L., Pritzkow, S., Shah Nawaz, M., Farris, C. M., and Soto, C. (2023). Seed amplification assay for the detection of pathologic alpha-synuclein aggregates in cerebrospinal fluid. *Nat. Protoc.* 18, 1179–1196. doi: 10.1038/s41596-022-00787-3
- Constatidines, V. C., Majbour, N. K., Paraskevass, G. P., Abdi, I., Safieh-Garabedian, B., Stefanis, L., et al. (2021). Cerebrospinal fluid alpha-synuclein species in cognitive and movements disorders. *Brain Sci.* 11:119. doi: 10.3390/brainsci11010119
- Coughlin, D., Xie, S. X., Liang, M., Williams, A., Peterson, C., Weintraub, D., et al. (2019). Cognitive and pathological influences of tau pathology in Lewy body disorders. *Ann. Neurol.* 85, 259–271. doi: 10.1002/ana.25392
- Coughlin, D. G., and Irwin, D. J. (2023). Fluid and biopsy based biomarkers in Parkinson's disease. *Neurotherapeutics* 20, 932–954. doi: 10.1007/s13311-023-01379-z
- Cressatti, M., Juwara, L., Galindez, J. M., Velly, A. M., and Nkurunziza, E. S. (2020). Salivary microR-153 and microR-223 levels as potential diagnostic biomarkers of idiopathic Parkinson's disease. *Mov. Disord.* 35, 468–477. doi: 10.1002/mds.27935
- Daniele, S., Frosini, D., Pietrobono, D., Petrozzi, L., Lo Gerfo, A., Baldacci, F., et al. (2018). α -synuclein heterocomplexes with β -amyloid are increased in red blood cells of Parkinson's disease patients and correlate with disease severity. *Front. Mol. Neurosci.* 11:53. doi: 10.3389/fnmol.2018.00053
- de Araujo, F. M., Cuenca-Bermejo, L., Fernandez-Villalba, E., Costa, S. L., Silva, V. D. A., and Herrero, M. T. (2021). Role of microgliosis and NLRP3 inflammasome in Parkinson's disease pathogenesis and therapy. *Cell. Mol. Neurobiol.* 42, 1283–1300. doi: 10.1007/s10571-020-01027-6
- De Bartolo, M. I., Vivacqua, G., Belvisi, D., Gaetani, L., Giannini, G., Mancinelli, R., et al. (2023). A combined panel of salivary biomarkers in *de novo* Parkinson's disease. *Ann. Neurol.* 93, 446–459. doi: 10.1002/ana.26550
- Delenclos, M., Jones, D. R., McLean, P. J., and Uitti, R. J. (2016). Biomarkers in Parkinson's disease: advances and strategies. *Parkinsonism Relat. Disord.* 22, S106–S110. doi: 10.1016/j.parkreldis.2015.09.048
- Delgado-Alvarado, M., Gago, B., Gorostidi, A., Jimenez Urbieto, H., Dacosta-Aguayo, R., et al. (2017). Tau/alpha-synuclein ratio and inflammatory proteins in Parkinson's disease: an exploratory study. *Mov. Disord.* 32, 1066–1073. doi: 10.1002/mds.27001
- Delgado-Alvarado, M., Gago, B., Navalpotro-Gomez, I., Jiménez-Urbieto, H., and Rodriguez-Oroz, M. C. (2016). Biomarkers for dementia and mild cognitive impairment in Parkinson's disease. *Mov. Disord.* 31, 861–881. doi: 10.1002/mds.26662
- Devic, I., Hwang, H., Edgar, J. S., Izutsu, K., Presland, R., Pan, C., et al. (2011). Salivary alpha-synuclein and DJ-1: Potential biomarkers for Parkinson's disease. *Brain* 134:e178. doi: 10.1093/brain/awr015
- Dixit, A., Mehta, R., and Singh, A. K. (2019). Proteomics in human Parkinson's disease: present scenario and future directions. *Cell. Mol. Neurobiol.* 39, 901–915. doi: 10.1007/s10571-019-00700-9
- Duran, R., Barrero F. J., Morales, B., Luna J. D., Ramirez, M., and Vives, F. (2010). Plasma alpha-synuclein in patients with Parkinson's disease with and without treatment. *Mov. Disord.* 25, 489–493. doi: 10.1002/mds.22928
- Dutta, S., Hornung, S., Kruyatidee, A., Maina, M. B., Delanghe, N., Delputte, C., et al. (2021). Alpha-synuclein in blood exosomes immunoprecipitated using neuronal and oligodendroglial markers distinguishes Parkinson's disease from multiple system atrophy. *Acta Neuropathol.* 142, 495–511. doi: 10.1007/s00401-021-02324-0
- Eidson, L. N., Kannarkat, G. T., Barnum, C. J., Chang, J., Chung, J., Caspell-Garcia, C., et al. (2017). Candidate inflammatory biomarkers display unique relationships with alpha-synuclein and correlate with measures of disease severity in subjects with Parkinson's disease. *J. Neuroinflammation* 14:164. doi: 10.1186/s12974-017-0935-1
- El-Agnaf, O. M., Salem, S. A., Paleologou, K. E., Curran, M. D., Gibson, M. J., Court, J. A., et al. (2006). Detection of oligomeric forms of alpha-synuclein protein in human plasma as a potential biomarker for Parkinson's disease. *FASEB J.* 20, 419–425. doi: 10.1096/fj.03-1449com
- Eusebi, P., Giannandrea, D., Biscetti, L., Abbraha, I., Chiasserini, D., Orso, M., et al. (2017). Diagnostic utility of cerebrospinal fluid α -synuclein in Parkinson's disease: a systematic review and meta-analysis. *Mov. Disord.* 32, 1389–1400. doi: 10.1002/mds.27110
- Fairfoul, G., McGuire, L. I., Pal, S., Ironside, J. W., Neumann, J., Christie, S., et al. (2016). Alpha-synuclein RT-QuIC in the CSF of patients with alpha-synucleinopathies. *Ann. Clin. Transl. Neurol.* 3, 812–818. doi: 10.1002/acn3.338
- Fan, Z., Pan, Y. T., Zhang, Z. Y., Yang, H., Yu, S. Y., Zheng, Y., Ma, J. H., et al. (2020). Systemic activation of NLRP3 inflammasome and plasma alpha-synuclein levels are correlated with motor severity and progression in Parkinson's disease. *J. Neuroinflammation* 17:11. doi: 10.1186/s12974-019-1670-6
- Fereshtehnejad, S. M., Romenets, S. R., Anang, J. B., Latreille, V., Gagnon, J. F., and Postuma, R. B. (2015). New clinical subtypes of Parkinson disease and their longitudinal progression: a prospective cohort comparison with other phenotypes. *JAMA Neurol.* 72, 863–873. doi: 10.1001/jamaneurol.2015.0703
- Fereshtehnejad, S. M., Zeighami, Y., Dagher, A., and Postuma, R. B. (2017). Clinical criteria for subtyping Parkinson's disease: biomarkers and longitudinal progression. *Brain* 140, 1959–1976. doi: 10.1093/brain/awx118
- Forland, M. G., Tysnes, O. B., Aarsland, D., Maple-Grodem, J., Pedersen, K. F., Alves, G., et al. (2020). The value of cerebrospinal fluid α -synuclein and the tau/ α -synuclein ratio for diagnosis of neurodegenerative disorders with Lewy pathology. *Eur. J. Neurol.* 27, 43–50. doi: 10.1111/ene.14032
- Foulds, P. G., Yokota, O., Thurston, A., Davidson, Y., Ahmed, Z., Holton, J., et al. (2012). Post mortem cerebrospinal fluid α -synuclein levels are raised in multiple system atrophy and distinguish this from the other α -synucleinopathies, Parkinson's disease and Dementia with Lewy bodies. *Neurobiol. Dis.* 45, 188–195. doi: 10.1016/j.nbd.2011.08.003
- Fraser, K. B., Rawlins, A. B., Clark, R. G., Alcalay, R. N., Standaert, D. G., Liu, N., et al. (2016). Ser(P)-1292 LRRK2 in urinary exosomes is elevated in idiopathic Parkinson's disease: P-LRRK2 predicts severity of PD. *Mov. Disord.* 31, 1543–1550. doi: 10.1002/mds.26686
- Fu, Y., Jiang, C., Tofaris, G. K., and Davis, J. J. (2020). Facile impedimetric analysis of neuronal exosome markers in Parkinson's disease diagnostics. *Anal. Chem.* 92, 13647–13651. doi: 10.1021/acs.analchem.0c03092
- Ganguly, U., Singh, S., Pal, S., Prasad, S., Agrawal, B. K., Saini, R. V., et al. (2021). Alpha-synuclein as a biomarker of Parkinson's disease: good, but not good enough. *Front. Aging Neurosci.* 13:702639. doi: 10.3389/fnagi.2021.702639
- Garrido, A., Fairfoul, G., Tolosa, E. S., Martí, M. J., and Green, A. (2019). α -synuclein RT-QuIC in cerebrospinal fluid of LRRK2-linked Parkinson's disease. *Ann. Clin. Transl. Neurol.* 6, 1024–1032. doi: 10.1002/acn3.772
- Giampa, M., Amundarain, M. J., Herrera, M. G., Tonali, N., and Donero, V. I. (2021). Implementing complementary approach to shape the mechanism of α -synuclein oligomerization as a model of amyloid aggregation. *Molecular* 27:88. doi: 10.3390/molecules27010088
- Goldman, J. G., Andrews, H., Amara, A., Naito, A., Alcalay, R. N., Shaw, L. M., et al. (2018). Cerebrospinal fluid, plasma, and saliva in the BioFIND study: relationships among biomarkers and Parkinson's disease features. *Mov. Disord.* 33, 282–288. doi: 10.1002/mds.27232
- Grossauer, A., Hemicker, G., Krismer, F., Peball, M., Djamshidian, A., Poewe, W., et al. (2023). α -Synuclein seed amplification assays in the diagnosis of synucleinopathies using cerebrospinal fluid—a systematic review and meta-analysis. *Mov. Disord. Clin. Pract.* 10, 737–747. doi: 10.1002/mdc3.13710
- Groveman, B. R., Orru, C. D., Hughson, A. G., Raymond, L. D., Zanuso, G., Ghetti, B., et al. (2018). Rapid and ultra-sensitive quantitation of disease-associated alpha-synuclein seeds in brain and cerebrospinal fluid by alphaSyn RT-QuIC. *Acta Neuropathol. Commun.* 6:7. doi: 10.1186/s40478-018-0508-2
- Guévremont, D., Roy, J., Cutfield, N. J., and Williams, J. M. (2023). MicroRNAs in Parkinson's disease: a systematic review and diagnostic accuracy meta-analysis. *Sci. Rep.* 13:16272. doi: 10.1038/s41598-023-43096-9
- Gupta, V., Garg, R. K., and Khattri, S. (2016). Levels of IL-8 and TNF-alpha decrease in Parkinson's disease. *Neurol. Res.* 38, 98–102. doi: 10.1080/01616412.2015.1133026
- Gurgone, A., Cardinale, V., Tangari, M. M., Budicin, S., Comai, D., Ledda, C., et al. (2026). Clinical validation of α -synuclein in salivary extracellular vesicles as a biomarker for Parkinson's disease: a longitudinal study. *Eur. J. Neurol.* 33:e70508. doi: 10.1111/ene.70508
- Guzowska, J., Kowalski, S., Schachta, I., Piekus-Slomka, N., and Slomka, A. (2026). Connecting the dots: milestones in the history of extracellular vesicle research. *Int. J. Mol. Sci.* 27:2470. doi: 10.3390/ijms27052470
- Hall, S., Janelidze, S., Surova, Y., Widner, H., Zetterberg, H., and Hansson, O. (2018). Cerebrospinal fluid concentrations of inflammatory markers in Parkinson's disease and atypical parkinsonian disorders. *Sci. Rep.* 8:13276. doi: 10.1038/s41598-018-31517-z
- Hall, S., Surova, Y., Öhrfelt, A., Blennow, K., Zetterberg, H., Hansson, O. the Swedish BioFIND, R., et al. (2026). Longitudinal measurements of cerebrospinal fluid biomarkers in Parkinson's disease. *Mov. Disord.* 31, 898–905. doi: 10.1002/mds.26578
- Hall, S., Surova, Y., Öhrfelt, A., Zetterberg, H., and Lindqvist, D., Hansson, O. (2015). CSF biomarkers and clinical progression of Parkinson disease. *Neurology* 84, 57–63. doi: 10.1212/WNL.0000000000001098
- Halliday, G., Hely, M., Reid, W., and Morris, J. (2008). The progression of pathology in longitudinally followed patients with Parkinson's disease. *Acta Neuropathol.* 115, 409–415. doi: 10.1007/s00401-008-0344-8

- Hamm-Alvarez, S. F., Okamoto, C. T., Janga, S. R., Feigenbaum, D., Edman, M. C., Freire, D., et al. (2019). Oligomeric alpha-synuclein is increased in basal tears of Parkinson's patients. *Biomark. Med.* 13, 941–952. doi: 10.2217/bmm-2019-0167
- Hansson, O., Hall, S., Ohrfelt, A., Zetterberg, H., Blennow, K., Minthon, L., et al. (2014). Levels of cerebrospinal fluid α -synuclein oligomers are increased in Parkinson's disease with dementia and dementia with Lewy bodies compared to Alzheimer's disease. *Alzheimers. Res. Ther.* 6:25. doi: 10.1186/alzrt255
- Hansson, O., Janelidze, S., Hall, S., Magdalinou, N., Lima Dias, S., Constantinescu, R., et al. (2017). Blood-based NFL: a biomarker for differential diagnosis of parkinsonian disorders. *Lancet Neurol.* 16, 551–560. doi: 10.1016/S1474-4422(17)30124-2
- Harischandra, D. S., Ghaisas, S., Rokad, D., Zamanian, M., Jin, H., Anantharam, V., et al. (2018). Environmental neurotoxicant manganese regulates exosome-mediated extracellular miRNAs in a cell culture model of Parkinson's disease. *Neurotoxicology* 64, 267–277. doi: 10.1016/j.neuro.2017.04.007
- Hatano, T., Okuzumi, A., Matsumoto, G., Tsunemi, T., and Hattori, N. (2024).
- Henderson, M. X., Sengupta, M., Trojanowski, J. Q., and Lee, V. M. Y. (2019). Alzheimer's disease tau is a prominent pathology in LRRK2 Parkinson's disease. *Acta Neuropathol. Commun.* 7:183. doi: 10.1186/s40478-019-0836-x
- Herbert, M. K., Aerts, M. B., Beenes, M., Netea-Maier, R. T., Esselink, R. A., Bloem, B. R., et al. (2015). CSF neurofilament light chain is a biomarker of MSA and PSP, but not PD and DLB. *Front. Neurol.* 6:91. doi: 10.3389/fneur.2015.00091
- Hook, V., Podvin, S., Mosier, C., Boyarko, B., Seyffert, L., Stringer, H., et al. (2023). Emerging evidence for dysregulated proteome cargoes of tau-propagating extracellular vesicles driven by familial mutations of tau and presenilin. *Extracell. Vesicles Circ. Nucl. Acids* 4, 588–598. doi: 10.20517/evncna.2023.44
- Howlett, D. R., Whitfield, D., Johnson, M., Attems, J., O'Brien, J. T., Aarsland, D., et al. (2015). Regional multiple pathology scores are associated with cognitive decline in lewy body dementias. *Brain Pathol.* 25, 401–408. doi: 10.1111/bpa.12182
- Hu, W. T., Howell, J. C., Ozturk, T., Gangishetti, U., Kollhoff, A. L., Gangishetti, U., Kollhoff, A. L., Hatcher-Martin, J. M., Tsvetkova, D. Z., et al. (2019). CSF cytokines in aging, multiple sclerosis, and dementia. *Front. Immunol.* 10:480. doi: 10.3389/fimmu.2019.00480
- Hu, X., Yang, Y., and Gong, D. (2017). Changes of cerebrospinal fluid A β 42, t-tau, and p-tau in Parkinson's disease patients with cognitive impairment relative to those with normal cognition: a meta-analysis. *Neurol. Sci.* 38, 1953–1961. doi: 10.1007/s10072-017-3088-1
- Hu, Y., Yu, S. Y., Zuo, L. J., Cao, C. J., Wang, F., Chen, Z. J., et al. (2015). Parkinson disease with REM sleep behavior disorder: features, alpha-synuclein, and inflammation. *Neurology* 84, 888–894. doi: 10.1212/WNL.0000000000001308
- Irwin, D. J., Coughlin, D., Nevler, N., Akhtar, R. S., McMillan, C. T., Lee, E. B., et al. (2017). Antemortem CSF tau and a beta biomarkers are predictive of postmortem alzheimer's disease pathology in autopsy confirmed lewy body disease. *Ann. Neurol.* 81, S56–S56.
- Irwin, D. J., Fedler, J., Coffey, C. S., Caspell-Garcia, C., Kang, J. H., Simuni, T., et al. (2020). Evolution of Alzheimer's disease cerebrospinal fluid biomarkers in early Parkinson's disease. *Ann. Neurol.* 88, 574–587. doi: 10.1002/ana.25811
- Irwin, D. J., Lee, V. M.-Y., and Trojanowski, J. Q. (2013). Parkinson's disease dementia: convergence of α -synuclein, tau and amyloid- β pathologies. *Nat. Rev. Neurosci.* 14, 626–636. doi: 10.1038/nrn3549
- Ishiguro, Y., Tsunemi, T., Shimada, T., Saito, K., Furukawa, Y., Hatano, T., et al. (2024). Extracellular vesicles contain filamentous alpha-synuclein and facilitate the propagation of Parkinson's pathology. *Biochem. Biophys. Res. Commun.* 703:149620. doi: 10.1016/j.bbrc.2024.149620
- Ishiki, A., Kamada, M., Kawamura, Y., Terao, C., Shimoda, F., Tomita, N., et al. (2016). Glial fibrillary acidic protein in the cerebrospinal fluid of alzheimer's disease, dementia with lewy bodies, and frontotemporal lobar degeneration. *J. Neurochem.* 136, 258–261. doi: 10.1111/jnc.13399
- Iwaoka, K., Otsuka, C., Maeda, T., Yamahara, K., Kato, K., Takahashi, M., and Yamada, K. (2020). Impaired metabolism of kynurenine and its metabolites in CSF of Parkinson's disease. *Neurosci. Lett.* 714:134576. doi: 10.1016/j.neulet.2019.134576
- Jellinger, K. A. (2008). Neuropathological aspects of Alzheimer disease, Parkinson disease and frontotemporal dementia. *Neurodegener. Dis.* 5, 118–121. doi: 10.1159/000113679
- Jellinger, K. A., Seppi, K., Wenning, G. K., and Poewe, W. (2002). Impact of coexistent Alzheimer pathology on the natural history of Parkinson's disease. *J. Neural Transm.* 109, 329–339. doi: 10.1007/s007020200027
- Jiang, C., Hopfner, F., Katsikoudi, A., Hein, R., Catli, C., Evetts, S., et al. (2020). Serum neuronal exosomes predict and differentiate Parkinson's disease from atypical parkinsonism. *J. Neurol. Neurosurg. Psychiatr.* 91, 720–729. doi: 10.1136/jnnp-2019-322588
- Jiang, Y., Chen, J., Sun, Y., Li, F., Wei, L., Sun, W., et al. (2021). Profiling of differentially expressed microRNAs in Saliva of Parkinson's disease patients. *Front. Neurol.* 12:738530.
- Jin, H., Gu, H.Y., Mao, C.J., Chen, J., Liu, C.F. (2020). Association of inflammatory factors and aging in Parkinson's disease. *Neurosci. Lett.* 736:135259. doi: 10.3389/fneur.2021.738530
- Kaerst, L., Kuhlmann, A., Wedekind, D., Stoeck, K., Lange, P., and Zerr, I. (2013). Using cerebrospinal fluid marker profiles in clinical diagnosis of dementia with lewy bodies, Parkinson's Disease, and Alzheimer's Disease. *J. Alzheimer Dis* 38, 63–73. doi: 10.3233/JAD-130995
- Kang, J.-H., Mollenhauer, B., Coffey, C. S., Toledo, J. B., Weintraub, D., Galasko, D. R., et al. (2016). CSF biomarkers associated with disease heterogeneity in early Parkinson's disease: the Parkinson's progression markers initiative study. *Acta Neuropathol.* 131, 935–949. doi: 10.1007/s00401-016-1552-2
- Kang, J. H., Irwin, D. J., Chen-Plotkin, A. S., Siderowf, A., Caspell, C., Coffey, C. S., et al. (2013). Association of cerebrospinal fluid beta-amyloid 1–42, T-tau, P-tau181, and alpha-synuclein levels with clinical features of drug-naïve patients with early Parkinson disease. *JAMA Neurol.* 70, 1277–1287. doi: 10.1001/jamaneurol.2013.3861
- Kang, U. J., Boehme, A. K., Fairfoul, G., Shahnawaz, M., Ma, T. C., Hutten, S. J., et al. (2019). Comparative study of cerebrospinal fluid alpha-synuclein seeding aggregation assays for diagnosis of Parkinson's disease. *Mov. Disord.* 34, 536–544. doi: 10.1002/mds.27646
- Karpenko, M. N., Vasilishina, A. A., Gromova, E. A., Muruzheva, Z. M., Miliukhina, I. V., and Bernadotte, A. (2018). Interleukin-1beta, interleukin-1 receptor antagonist, interleukin-6, interleukin-10, and tumor necrosis factor-alpha levels in CSF and serum in relation to the clinical diversity of Parkinson's disease. *Cell. Immunol.* 327, 77–82. doi: 10.1016/j.cellimm.2018.02.011
- Keighron, C. N., Avazadeh, S., Goljanek-Whysall, K., McDonagh, B., Howard, L., Ritter, T., et al. (2023). Extracellular Vesicles, Cell-Penetrating Peptides and miRNAs as Future Novel Therapeutic Interventions for Parkinson's and Alzheimer's Disease. *Biomedicine* 11:728. doi: 10.3390/biomedicine11030728
- Khalil, M., Teunissen, C. E., Lehmann, S., Otto, M., Piehl, F., Sormani, M. P., et al. (2024). Neurofilaments as biomarkers in neurological disorders: toward clinical application. *Nat. Rev. Neurol.* 20, 269–287. doi: 10.1038/s41582-024-00955-x
- Kharel, S., Ojha, R., Bist, A., Joshi, S. P., Rauniyar, R., and Yadav, J. K. (2022). Salivary alpha-synuclein as a potential fluid biomarker in Parkinson's disease: a systematic review and meta-analysis. *Aging Med.* 5, 53–62. doi: 10.1002/agm2.12192
- Kim, K. Y., Shin, K. Y., and Chang, K. A. (2024). Potential exosome biomarkers for Parkinson's disease diagnosis: a systematic review and meta-analysis. *Int. J. Mol. Sci.* 25:5307. doi: 10.3390/ijms25105307
- Kim, R., Kim, H. J., Kim, A., Jang, M., Kim, Y., Yoo, D., et al. (2018). Peripheral blood inflammatory markers in early Parkinson's disease. *J. Clin. Neurosci.* 58, 30–33. doi: 10.1016/j.jocn.2018.10.079
- Kluge, A., Schaeffer, E., Bunk, J., Sommerauer, M., Rütgen, S., Schulte, C., et al. (2024). Detecting misfolded α -synuclein in blood years before the diagnosis of Parkinson's disease. *Mov. Disord.* 39, 1289–1299. doi: 10.1002/mds.29766
- Koga, S., Sekiya, H., Kondru, N., Ross, O. A., and Dickson, D. W., (2021). Neuropathology and molecular diagnosis of synucleinopathies. *Mol. Neurodegener* 16:83. doi: 10.1186/s13024-021-00501-z
- Kouchaki, E., Kakhaki, R. D., Tamtaji, O. R., Dadgostar, E., Behnam, M., and Nikouinejad, H. (2018). Increased serum levels of TNF-alpha and decreased serum levels of IL-27 in patients with Parkinson disease and their correlation with disease severity. *Clin. Neurol. Neurosurg.* 166, 76–79. doi: 10.1016/j.clineuro.2018.01.022
- Kouli, A., and Williams-Gray, C. H. (2020). Timing is everything: the T-cell response to alpha-synuclein is maximal in early Parkinson's. *Mov. Disord.* 35:1137. doi: 10.1002/mds.28122
- Kurata, T., Kawarabayashi, T., Murakami, T., Nishimura, M., Morimoto, N., Kawai, H., et al. (2007). Enhanced accumulation of phosphorylated alpha-synuclein in double transgenic mice expressing mutant beta-amyloid precursor protein and presenilin-1. *J. Neurosci. Res.* 85, 2246–2252. doi: 10.1002/jnr.21352
- Latifkar, A., Hur, Y. H., Sanchez, J. C., Cerione, R. A., and Antonyak, M. A. (2019). New insights into extracellular vesicle biogenesis and function. *J. Cell Sci.* 132:jcs222406. doi: 10.1242/jcs.222406
- Leaver, K., and Poston, K. L. (2015). Do CSF biomarkers predict progression to cognitive impairment in Parkinson's disease patients? A systematic review. *Neuropsychol. Rev.* 25, 411–423. doi: 10.1007/s11065-015-9307-8
- Lee, A., and Gilbert, R. M. (2016). Epidemiology of Parkinson's disease. *Neurol. Clin.* 34, 955–966. doi: 10.1016/j.ncl.2016.06.012
- Lerche, S., Zimmermann, M., Wursterl Roeben, B., Fries, F.L., Deuschle, C., et al. (2022). CSF and serum levels of inflammatory markers in PD: Sparse correlation, sex differences and association with neurodegenerative biomarkers. *Front. Neurol.* 13:834580.
- Li, P. Y., Xu, P. Y., and Li, J. (2021). Editorial: biomarkers and pathogenesis of alpha Synuclein in Parkinson's disease. *Front. Aging Neurosci.* 13:776873. doi: 10.3389/fnagi.2021.776873

- Li, X., Yang, W., Li, X., Li, X., Chen, Z., Wang, C., et al. (2019). Levels of oligomeric alpha-synuclein in red blood cells are elevated in patients with Parkinson's disease and affected by brain alpha-synuclein expression. *Int. J. Clin. Exp. Med.* 12, 10470–10477.
- Li, X. Y., Li, W., Li, X., Li, X. R., Sun, L., Yang, W., et al. (2021). Alterations of erythrocytic phosphorylated alpha-synuclein in different subtypes and stages of Parkinson's disease. *Front. Aging Neurosci.* 13:623977. doi: 10.3389/fnagi.2021.623977
- Li, Y., Cao, Y., Liu, W., Chen, F., Zhang, H., Zhou, H., et al. (2024). Candidate biomarkers of EV- microRNA in detecting REM sleep behavior disorder and Parkinson's disease. *NPJ Parkinsons Dis.* 10:18. doi: 10.1038/s41531-023-00628-4
- Li, Y., Yang, Y., Zhao, A., Luo, N., Niu, M., Kang, W., et al. (2022). Parkinson's disease peripheral immune biomarker profile: a multicentre, cross-sectional and longitudinal study. *J. Neuroinflammation* 19:116. doi: 10.1186/s12974-022-02481-3
- Lian, T. H., Guo, P., Zuo, L. J., Hu, Y., Yu, S. Y., Yu, Q. J., et al. (2019). Tremor-dominant in Parkinson disease: the relevance to iron metabolism and inflammation. *Front. Neurosci.* 13:255. doi: 10.3389/fnins.2019.00255
- Liddel, S. A., and Barres, B. A. (2017). Reactive astrocytes: production, function, and therapeutic potential. *Immunity* 46, 957–967. doi: 10.1016/j.immuni.2017.06.006
- Lin, C. H., Li, C. H., Yang, K. C., Lin, F. J., Wu, C. C., Chieh, J. J., et al. (2019a). Blood NFL: a biomarker for disease severity and progression in Parkinson disease. *Neurology* 93, e1104–e1111. doi: 10.1212/WNL.0000000000008088
- Lin, C. H., Liu, H. C., Yang, S. Y., Yang, K. C., Wu, C. C., and Chiu, M. J. (2019b). Plasma pS129- α -Synuclein is a surrogate biofluid marker of motor severity and progression in Parkinson's disease. *J. Clin. Med.* 8:1601. doi: 10.3390/jcm8101601
- Lin, C. H., Yang, S. Y., Horng, H. E., Yang, C. C., Chieh, J. J., Chen, H. H., et al. (2017). Plasma α -synuclein predicts cognitive decline in Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry* 88, 818–824. doi: 10.1136/jnnp-2016-314857
- Lin, J., Ou, R., Li, C., Hou, Y., Wei, Q., Cao, B., et al. (2023). Plasma glial fibrillary acidic protein as a biomarker of disease progression in Parkinson's disease: a prospective cohort study. *BMC Med.* 21:420. doi: 10.1186/s12916-023-03120-1
- Lin, J., Zhang, M., Yu, C. Q., Xue, M., and Hu, P. P. (2025). Early diagnosis of Parkinson's disease: biomarker study. *Front. Aging Neurosci.* 17:1495769. doi: 10.3389/fnagi.2025.1495769
- Lindestam Arleham, C. S., Dhanwani, R., Pham, J., Kuan, R., Frazier, A., et al. (2020). Alpha Synuclein-specific T cell reactivity is associated with preclinical and early Parkinson's disease. *Nat. Commun.* 11:1875. doi: 10.1038/s41467-020-15626-w
- Lindqvist, D., Hall, S., Surova, Y., Nielsen, H. M., Janelidze, S., Brundin, L., et al. (2013). Cerebrospinal fluid inflammatory markers in Parkinson's disease—associations with depression, fatigue, and cognitive impairment. *Brain. Behav. Immun.* 33, 183–189.
- Liu, T., Zuo, H., Ma, D., Song, D., Zhao, Y., and Cheng, O. (2023). Cerebrospinal fluid GFAP is a predictive biomarker for conversion to dementia among *de novo* Parkinson's disease patients. *J. Neuroinflammation* 20:167. doi: 10.1186/s12974-023-02843-5
- Lotankar, S., Prabhavalkar, K. S., and Bhatt, L. K. (2017). Biomarkers for Parkinson's disease: recent advancement. *Neurosci. Bull.* 33, 585–597. doi: 10.1007/s12264-017-0183-5
- Luo, H., Yu, X., Li, P., Hu, J., Li, W., Li, X., et al. (2024). Different neurotoxicity and seeding activity between α -synuclein oligomers formed in plasma of patients with Parkinson's disease and multiple system atrophy. *Neuroscience* 557, 1–11. doi: 10.1016/j.neuroscience.2024.08.006
- Ma, J., Tang, Z., Wu, Y., Liu, Y., Zhang, H., Wang, X., et al. (2025). Differences in blood and cerebrospinal fluid between Parkinson's disease and related disorders. *Cell. Mol. Neurobiol.* 45, 1–15. doi: 10.1007/s10571-024-01523-z
- Ma, L. Z., Zhang, C., Wang, H., Ma, Y. H., Shen, X. N., Wang, J., et al. (2021). Serum neurofilament dynamics predicts cognitive progression in *de novo* Parkinson's disease. *J. Parkinsons Dis.* 11, 1117–1127. doi: 10.3233/JPD-212535
- Ma, Y., Farris, C. M., Weber, S., Wang, Z., Soto, C., Kang, U. J., et al. (2024). Sensitivity and specificity of a seed amplification assay for diagnosis of multiple system atrophy: a multicentre cohort study. *Lancet Neurol.* 23, 1225–1237. doi: 10.1016/S1474-4422(24)00395-8
- Maass, F., Rikker, S., Dambeck, V., Schäfer, J., Kwieciński, H., Schlüter, H., et al. (2020). Increased alpha-synuclein tear fluid levels in patients with Parkinson's disease. *Sci. Rep.* 10:8507. doi: 10.1038/s41598-020-65503-1
- Magdalino, N. K., Noyce, A. J., Pinto, R., Lindstrom, E., Holmen-Larsson, J., et al. (2017). Identification of candidate cerebrospinal fluid biomarkers in parkinsonism using quantitative proteomics. *Parkinsonism. Relat. Disord.* 37, 65–71. doi: 10.1016/j.parkreldis.2017.01.016
- Magdalino, N. K., Paterson, R. W., Schott, J. M., Fox, N. C., Mummery, C., Blennow, K., et al. (2015). A panel of nine cerebrospinal fluid biomarkers may identify patients with atypical parkinsonian syndromes. *J. Neurol. Neurosurg. Psychiatr.* 86, 1240–1247. doi: 10.1136/jnnp-2014-309562
- Maiese, K. (2022). Biomarkers for Parkinson's disease and neurodegenerative disorders: a role for non-coding RNAs. *Curr. Neurovasc. Res.* 19, 127–130. doi: 10.2174/1567202619666220602125806
- Majbour, N., Msc, N. N. V., Eusebi, P., Chiasserini, D., Ardah, M., Varghese, S., et al. (2016). Longitudinal changes in CSF alpha-synuclein species reflect Parkinson's disease progression. *Mov. Disord.* 31, 1535–1542. doi: 10.1002/mds.26754
- Majbour, N. K., Aasly, J. O., Husta, E., Thomas, M. A., Vaikath, N. N., Eliezer, D., et al. (2020). CSF total and oligomeric α -Synuclein along with TNF- α as risk biomarkers for Parkinson's disease: a study in LRRK2 mutation carriers. *Transl. Neurodegener.* 9:15. doi: 10.1186/s40035-020-00192-4
- Majbour, N. K., Abdi, I. Y., Dakna, M., Vaikath, N. N., Ardah, M. T., Van Dijk, K. D., et al. (2021). Cerebrospinal α -synuclein oligomers reflect disease motor severity in DeNoPa longitudinal cohort. *Mov. Disord.* 36, 2048–2056. doi: 10.1002/mds.28611
- Majbour, N. K., Vaikath, N. N., van Dijk, K. D., Ardah, M. T., Vesterager, L. B., et al. (2016). Oligomeric and phosphorylated alpha-synuclein as potential CSF biomarkers for Parkinson's disease. *Mol. Neurodegener.* 11:7. doi: 10.1186/s13024-016-0072-9
- Mao, C., Wang, Y., Cui, S., and Xu, X. (2023). Association of serum neurofilament light chain and glial fibrillary acidic protein levels with cognitive decline in Parkinson's disease. *Brain Res.* 1805:148271. doi: 10.1016/j.brainres.2023.148271
- Margis, R., Margis, R., and Rieder, C. R. (2011). Identification of blood microRNAs associated to Parkinson disease. *J. Biotechnol.* 152, 96–101. doi: 10.1016/j.jbiotec.2011.01.023
- Martin-Ruiz, C., Williams-Gray, C. H., Yarnall, A. J., Boucher, J. J., Lawson, R. A., Fandaca, M. O., et al. (2020). Senescence and inflammatory markers for predicting clinical progression in Parkinson's disease: the ICICLEPD study. *J. Parkinsons. Dis.* 10, 193–206. doi: 10.3233/JPD-191724
- Meloni, M., Agliardi, C., Guerini, F. R., Zanzottera, M., Bolognesi, M., and Bruni, A. C. (2023). Oligomeric alpha-synuclein and tau aggregates in NDEVs differentiate Parkinson's disease from atypical parkinsonisms. *Neurobiol. Dis.* 176:105947. doi: 10.1016/j.nbd.2022.105947
- Miliukhina, I. V., Usenko, T. S., Senkevich, K. A., Nikolaev, M. A., Timofeeva, A. A., Kolesnikova, T. O., et al. (2020). Plasma cytokines profile in patients with Parkinson's disease associated with mutations in GBA gene. *Bull. Exp. Biol. Med.* 168, 423–426. doi: 10.1007/s10517-020-04723-x
- Miyamoto, K., S., and Saiki, H., Matsumoto, S., Imamichi, Y., Yamamoto, M., et al. (2022). Systemic metabolic alteration dependent on the thyroid-liver axis in early PD. *Ann. Neurol.* 93, 21. doi: 10.1002/ana.26510
- Mollenhauer, B., Caspell-Garcia, C. J., Coffey, C. S., Taylor, P., Shaw, L. M., Galasko, D. R., et al. (2017). Longitudinal CSF biomarkers in patients with early Parkinson disease and healthy controls. *Neurology* 89, 1959–1969. doi: 10.1212/WNL.0000000000004609
- Mollenhauer, B., Locascio, J. J., Schulz-Schaeffer, W., Sixel-Döring, F., Trenkwalder, C., and Schlossmacher, M. G. (2011). Alpha-synuclein and tau concentrations in cerebrospinal fluid of patients presenting with parkinsonism: a cohort study. *Lancet. Neurol.* 10, 230–240. doi: 10.1016/S1474-4422(11)70014-X
- Mollenhauer, B., Ms, C. J. C., Coffey, C. S., Taylor, P., Singleton, A., Galasko, D., et al. (2019). Longitudinal analyses of cerebrospinal fluid α -Synuclein in prodromal and early Parkinson's disease. *Mov. Disord.* 34, 1354–1364. doi: 10.1002/mds.27806
- Mollenhauer, B., Zimmermann, J., Sixel-Döring, F., Focke, N. K., Wicke, T., DeNoPa Study Group. (2019). Baseline predictors for progression 4 years after Parkinson's disease diagnosis in the De Novo Parkinson Cohort (DeNoPa). *Mov. Disord.* 34, 67–77. doi: 10.1002/mds.27492
- Montine, T. J., Shi, M., Quinn, J. F., Peskind, E. R., Craft, S., Ghingina, C., et al. (2010). CSF A β 42 and tau in Parkinson's disease with cognitive impairment. *Mov. Disord.* 25, 2682–2685. doi: 10.1002/mds.23287
- Nayak, A., Salt, G., Verma, S. K., and Kishore, U. (2015). Proteomics approach to identify biomarkers in neurodegenerative diseases. *Int. Rev. Neurobiol.* 121, 59–86. doi: 10.1016/bs.irn.2015.05.003
- Nie, C. Y., Sun, H., Zhen, Zhang, L., Wang, Y., Li, H., et al. (2020). Differential expression of plasma exo- miRNA in neurodegenerative diseases by next- generation sequencing. *Front. Neurosci.* 14, 438. doi: 10.3389/fnins.2020.00438
- Niemman, L., Lezius, S., Maceski, A., Leppert, D., Englisch, C., Schwedhelm, E., et al. (2021). Serum neurofilament is associated with motor function, cognitive decline and subclinical cardiac damage in advanced Parkinson's disease (MARK-PD). *Parkinsonism Relat. Disord.* 90, 44–48.
- Niu, M., Li, Y., Li, G., Chen, W., Zhang, J., Wang, X., et al. (2020). A longitudinal study on alpha-synuclein in plasma neuronal exosomes as a biomarker for Parkinson's disease development and progression. *Eur. J. Neurol.* 27, 967–974. doi: 10.1111/ene.14208
- Norman, M., Ter-Ovanesyan, D., Trieu, W., Lazarovits, R., Kowal, J., Lee, J. H., et al. (2021). L1CAM is not associated with extracellular vesicles in human cerebrospinal fluid or plasma. *Nat. Methods* 18, 631–634. doi: 10.1038/s41592-021-01174-8
- Oeckl, P., Halbgebauer, S., Anderl-Straub, S., Oeckl, P., Halbgebauer, S., Anderl-Straub, S., (2019). Glial fibrillary acidic protein in serum is increased in Alzheimer's disease and correlates with cognitive impairment. *J. Alzheimers. Dis.* 67, 481–488. doi: 10.3233/JAD-180325
- Ohmichi, T., Mitsuhashi, M., Tatebe, H., Kasai, T., El-Agnaf, O. M. A., and Tokuda, T. (2019). Quantification of brain-derived extracellular vesicles in plasma as a biomarker to diagnose Parkinson's and related diseases. *Parkinsonism. Relat. Dis.* 61, 82–87. doi: 10.1016/j.parkreldis.2018.11.021

- Okuzumi, A., Hatano, T., Matsumoto, G., Nojiri, S., Komatsu, M., Suzuki, M., et al. (2023). Propagative alpha-synuclein seeds as serum biomarkers for synucleinopathies. *Nat. Med.* 29, 1448–1455. doi: 10.1038/s41591-023-02358-9
- Olsson, B., Constantinescu, R., Holmberg, B., Andreasen, N., Blennow, K., and Zetterberg, H. (2013). The glial marker YKL-40 is decreased in synucleinopathies. *Mov. Disord.* 28, 1882–1885. doi: 10.1002/mds.25589
- Oosterveld, L. P., Verberk, I. M. W., Majbour, N. K., El-Agnaf, O. M., Weinstein, H. C., et al. (2020). CSF or serum neurofilament light added to alpha-synuclein panel discriminates Parkinson's from controls. *Mov. Disord.* 35, 288–295. doi: 10.1002/mds.27897
- Oueslati, A. (2016). Implication of alpha-synuclein phosphorylation at S129 in synucleinopathies: what have we learned in the past decade? *J. Parkinsons. Dis.* 6, 39–51. doi: 10.3233/JPD-160779
- Oueslati, A., Fournier, M., and Lashuel, H. A. (2010). Role of post-translational modifications in modulating the structure, function, and toxicity of alpha-synuclein: implications for Parkinson's disease pathogenesis and therapies. *Prog. Brain Res.* 183, 115–145. doi: 10.1016/S0079-6123(10)83007-9
- Pagonabarraga, J., Perez-Gonzalez, R., Bejr-Kasem, H., Gironell, A., García-Sánchez, C., Campdelacreu, J., et al. (2022). Dissociable contribution of plasma NfL and p-tau181 to cognitive impairment in Parkinson's disease. *Parkinsonism. Relat. Disord.* 105, 132–138. doi: 10.1016/j.parkreldis.2022.05.020
- Paoletti, F. P., Gaetani, L., and Parnetti, L. (2020). The challenge of disease-modifying therapies in Parkinson's disease: role of CSF Biomarkers. *Biomolecules* 10:335. doi: 10.3390/biom10020335
- Papagiannakis, N., Koros, C., Stamelou, M., Rizos, A., Xilouri, M., and Stefanis, L. (2018). Alpha-synuclein dimerization in erythrocytes of patients with genetic and non-genetic forms of Parkinson's disease. *Neurosci. Lett.* 672, 145–149. doi: 10.1016/j.neulet.2017.11.012
- Park, M. J., Cheon, S. M., Bae, H. R., Kim, S. H., and Kim, J. W. (2011). Elevated levels of alpha-synuclein oligomer in the cerebrospinal fluid of drug-naïve patients with Parkinson's disease. *J. Clin. Neurol.* 7, 215–222. doi: 10.3988/jcn.2011.7.4.215
- Parnetti, L., Farotti, L., Eusebi, P., Chiasserini, D., De Carlo, C., Giannandrea, D., et al. (2014). Differential role of CSF alpha-synuclein species, tau, and Aβ42 in Parkinson's disease. *Front. Aging Neurosci.* 6:53. doi: 10.3389/fnagi.2014.00053
- Parnetti, L., Gaetani, L., Eusebi, P., Paciotti, S., Parnetti, P., Chiasserini, D., et al. (2019). CSF and blood biomarkers for Parkinson's disease. *Lancet. Neurol.* 18, 573–586. doi: 10.1016/S1474-4422(19)30024-9
- Pedersen, C. C., Groden, J. M., and Lange, J. (2025). A systematic review of biofluid phosphorylated α-synuclein in Parkinson's disease. *Parkinsonism Relat. Disord.* 132:107240. doi: 10.1016/j.parkreldis.2024.107240
- Perner, C., Perner, F., Gaur, N., Zimmermann, S., Witte, O. W., and Storch, A. (2019). Plasma VCAM1 levels correlate with disease severity in Parkinson's disease. *J. Neuroinflammation* 16:94. doi: 10.1186/s12974-019-1482-8
- Pinotsi, D., Buell, A. K., Dobson, C. M., Kaminski Schierle, G.S., and Kaminski, C. F. (2013). A label-free, quantitative assay of amyloid fibril growth based on intrinsic fluorescence. *ChemBioChem* 14, 846–850. doi: 10.1002/cbic.201300103
- Poewe, W., Seppi, K., Tanner, C. M., Halliday, G. M., Brundin, P., Volkman, J., et al. (2017). Parkinson disease. *Nat. Rev. Dis. Prim.* 3:17013. doi: 10.1038/nrdp.2017.13
- Poggiolini, I., Gupta, V., Lawton, M., Rossi, M., Fazio, P., Picillo, M., et al. (2022). Diagnostic value of cerebrospinal fluid alpha-synuclein seed quantification in synucleinopathies. *Brain* 145, 584–595. doi: 10.1093/brain/awab431
- Postuma, R. B., Berg, D., Stern, M., Poewe, W., Olanow, C. W., Oertel, W. H., et al. (2015). MDS clinical diagnostic criteria for Parkinson's disease. *Mov. Disord.* 30, 1591–1601. doi: 10.1002/mds.26424
- Pötter-Nerger, M., Dutke, J., Lezius, S., Buhmann, C., Schulz, R., Gerloff, C., Kühle, J., Choe, C. U. (2022). Serum neurofilament light chain and postural instability/gait difficulty (PIGD) subtypes of Parkinson's disease in the MARK-PD study. *J. Neural Transm. (Vienna)* 129, 295–300. doi: 10.1007/s00702-022-02464-x
- Pouloupoulos, M., Levy, O. A., and Alcalay, R. N. (2012). The neuropathology of genetic Parkinson's disease. *Mov. Disord.* 27, 831–842. doi: 10.1002/mds.24962
- Qiu, X., Xiao, Y., Wu, J., Gan, L., Huang, Y., and Wang, J. (2019). C-reactive protein and risk of Parkinson's disease: a systematic review and meta-analysis. *Front. Neurol.* 10:384. doi: 10.3389/fneur.2019.00384
- Quek, C., and Hill, A. F. (2017). The role of extracellular vesicles in neurodegenerative diseases. *Biochem. Biophys. Res. Commun.* 483, 1178–1186. doi: 10.1016/j.bbrc.2016.09.090
- Rani, K., Mukherjee, R., Singh, E., Kumar, S., Sharma, V., Vishwakarma, P., et al. (2019). Neuronal exosomes in saliva of Parkinson's disease patients: a pilot study. *Parkinsonism Relat. Disord.* 67, 21–23. doi: 10.1016/j.parkreldis.2019.09.008
- Ransohoff, R. M. (2016). How neuroinflammation contributes to neurodegeneration. *Science* 353, 777–783. doi: 10.1126/science.aag2590
- Rastogi, S., Rani, K., Rai, S., Singh, R., Bharti, P. S., et al. (2023). Fluorescence-tagged salivary small extracellular vesicles as a nanotool in early diagnosis of Parkinson's disease. *BMC Med.* 21:335. doi: 10.1186/s12916-023-03031-1
- Rizzo, G., Copetti, M., Arcuti, S., Martino, D., and Logroscino, G. (2016). Accuracy of clinical diagnosis of Parkinson's disease: a systematic review and meta-analysis. *Neurology* 86, 566–576. doi: 10.1212/WNL.0000000000002350
- Rocha, N. P., Assis, F., Scalzo, P. L., Vieira, E. L. M., Barbosa, I. G., Teixeira, A. L., et al. (2018). Reduced activated T lymphocytes (CD4+CD25+) and plasma levels of cytokines in Parkinson's disease. *Mol. Neurobiol.* 55, 1488–1497. doi: 10.1007/s12035-017-0404-y
- Rochester, L., Galna, B., Lord, S., Yarnall, A., Morris, R., Duncan, G., et al. (2017). Decrease in Aβ42 predicts dopa-resistant gait progression in early Parkinson disease. *Neurology* 88, 1501–1511. doi: 10.1212/WNL.0000000000003840
- Rossi, M., Candelise, N., Baiardi, S., Mammana, A., Capellari, S., and Parchi, P. (2020). Ultrasensitive RT-QuIC assay with high sensitivity and specificity for Lewy body-associated synucleinopathies. *Acta Neuropathol.* 140, 49–62. doi: 10.1007/s00401-020-02160-8
- Russo, M. J., Orru, C. D., Concha-Marambio, L., Llanos, C., Cortes, J. M., Smirnov, I., et al. (2021). High diagnostic performance of independent alpha-synuclein seed amplification assays for detection of early Parkinson's disease. *Acta Neuropathol. Commun.* 9:179. doi: 10.1186/s40478-021-01292-6
- Sabaei, M., Rahimian, S., Haj Mohamad Ebrahim Ketabforoush, A., Rasoolijazi, H., Zamani, B., Rezaei, M., et al. (2023). Salivary levels of disease-related biomarkers in the early stages of Parkinson's and Alzheimer's disease: a cross-sectional study. *IBRO Neurosci. Rep.* 14, 285–292. doi: 10.1016/j.ibneur.2023.03.004
- Sabbagh, M. N., Adler, C. H., Lahti, T. J., Connor, D. J., Vedders, L., Peterson, L. K., et al. (2009). Parkinson disease with dementia: comparing patients with and without Alzheimer pathology. *Alzheimer Dis. Assoc. Disord.* 23, 295–297. doi: 10.1097/WAD.0b013e31819c5ef4
- Sanjari Moghaddam, H., Valitabar, Z., Ashraf-Ganjouei, A., Mojtahed Zadeh, M., Ghazi Sherbaf, F., and Aarabi, M. H. (2018). Cerebrospinal fluid C-reactive protein in Parkinson's disease: associations with motor and non-motor symptoms. *Neuromolecular. Med.* 20, 376–385. doi: 10.1007/s12017-018-8499-5
- Santaella, A., Kuiperij, H. B., van Rumund, A., Esselink, R. A. J., van Gool, A. J., and Verbeek, M. M. (2020). Inflammation biomarker discovery in Parkinson's disease and atypical parkinsonisms. *BMC Neurol.* 20:26. doi: 10.1186/s12883-020-1608-8
- Schmid, A. W., Fauvet, B., Moniatte, M., and Lashuel, H. A. (2013). Alpha-synuclein post-translational modifications as potential biomarkers for Parkinson disease and other synucleinopathies. *Mol. Cell. Proteomics* 12, 3543–3558. doi: 10.1074/mcp.R113.032730
- Schroder, J. B., Pawlowski, M., Meyer, Z., Horste, G., Gross, C. C., and Leypoldt, F. (2018). Immune cell activation in the cerebrospinal fluid of patients with Parkinson's disease. *Front. Neurol.* 9:1081. doi: 10.3389/fneur.2018.01081
- Schulz, I., Kruse, N., Gera, R. G., Kremer, T., Cedarbaum, J., and Berg, D. (2021). Systematic assessment of 10 biomarker candidates focusing on α-synuclein-related disorders. *Mov. Disord.* 36, 2874–2887. doi: 10.1002/mds.28738
- Shaheen, H., Sobhy, S., El Mously, S., Abuomira, M., and Mansour, M. (2020). Salivary alpha-synuclein (total and oligomeric form): potential biomarkers for Parkinson's disease. *Egypt. J. Neurol. Psychiatry Neurosurg.* 56:22. doi: 10.1186/s41983-020-0159-7
- Shi, M., Kovac, A., Korff, A., Cook, T. J., Ginghina, C., Bullock, K. M., et al. (2016). CNS tau efflux via exosomes is likely increased in Parkinson's disease but not in Alzheimer's disease. *Alzheimers Dement.* 12, 1125–1131. doi: 10.1016/j.jalz.2016.04.003
- Shi, M., Liu, C., Cook, T. J., Bullock, K. M., Zhao, Y., Ginghina, C., et al. (2014). Plasma exosomal alpha-synuclein is likely CNS-derived and increased in Parkinson's disease. *Acta Neuropathol.* 128, 639–650. doi: 10.1007/s00401-014-1314-y
- Si, X., Tian, J., Chen, Y., Yan, Y., Pu, J., and Zhang, B. (2019). Central nervous system-derived exosomal alpha-synuclein in serum may be a biomarker in Parkinson's disease. *Neuroscience* 413, 308–316. doi: 10.1016/j.neuroscience.2019.05.015
- Siderowf, A., Concha-Marambio, L., Lafontant, D. E., Farris, C. M., Ma, Y., Urenia, P. A., et al. (2023). Parkinson's progression markers initiative. Assessment of heterogeneity among participants in the Parkinson's progression markers initiative cohort using α-synuclein seed amplification: a cross-sectional study. *Lancet. Neurol.* 22, 407–417. doi: 10.1016/S1474-4422(23)00109-6
- Siderowf, A., Xie, S. X., Hurtig, H., Weintraub, D., Duda, J. E., Chen-Plotkin, A., et al. (2010). CSF amyloid beta 1-42 predicts cognitive decline in Parkinson disease. *Neurology* 75, 1055–1061. doi: 10.1212/WNL.0b013e3181f39a78
- Singer, W., Schmeichel, A. M., Shah Nawaz, M., Schmelzer, J. D., Boeve, B. F., Parisi, J. E., et al. (2020). Alpha-synuclein oligomers and neurofilament light chain in spinal fluid differentiate multiple system atrophy from lewy body synucleinopathies. *Ann. Neurol.* 88, 503–512. doi: 10.1002/ana.25824
- Sproviero, D. S., Gagliardi, S., Zucca, Borsani, G., and Lattuada, D. (2021). Different miRNA profiles in plasma derived small and large extracellular vesicles from patients with neurodegenerative diseases. *Int. J. Mol. Sci.* 22:08. doi: 10.3390/ijms22052737
- Stav, A. L., Aarsland, D., Johansen, K. K., Hessen, E., Auning, E., and Fladby, T. (2015). Amyloid-β and α-synuclein cerebrospinal fluid biomarkers and cognition in early Parkinson's disease. *Parkinsonism. Relat. Disord.* 21, 758–764. doi: 10.1016/j.parkreldis.2015.04.027

- Stewart, T., Sossi, V., Aasly, J. O., Appel-Cresswell, S., Martin, W. R. W., and Stoessl, A. J. (2015). Phosphorylated alpha-synuclein in parkinson's disease: correlation depends on disease severity. *Acta Neuropathol. Commun.* 3:7. doi: 10.1186/s40478-015-0185-3
- Stuendl, A., Kraus, T., Chatterjee, M., Greff, F. M., Schmid, B., Krause, S. M., et al. (2021). alpha-Synuclein in plasma-derived extracellular vesicles is a potential biomarker of Parkinson's disease. *Mov. Disord.* 36, 2508–2518. doi: 10.1002/mds.28639
- Stuendl, A., Kunadt, M., Kruse, N., Klucken, J. Koch, J. C. Giese, A., et al. (2016). Induction of alpha-synuclein aggregate formation by CSF exosomes from patients with Parkinson's disease and dementia with Lewy bodies. *Brain* 139, 481–494. doi: 10.1093/brain/awv346
- Su, W., Chen, H. B., Li, S. H., Zhang, X. Y., Wang, L., Liu, Y., et al. (2012). Correlational study of the serum levels of the glial fibrillary acidic protein and neurofilament proteins in Parkinson's disease patients. *Clin. Neurol. Neurosurg.* 114, 372–375. doi: 10.1016/j.clineuro.2011.11.002
- Sulzer, D., Alcalay, R. N., Garretti, F., Cote, L., Kanter, E., Greenspan, N. S., et al. (2017). T cells from patients with Parkinson's disease recognize alpha-synuclein peptides. *Nature* 546, 656–661. doi: 10.1038/nature22815
- Swallow, D. M. A., and Counsell, C. E. (2023). The evolution of diagnosis from symptom onset to death in progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) compared to Parkinson's disease (PD). *J. Neurol.* 270, 3464–3474. doi: 10.1007/s00415-023-11629-x
- Takov, K., Yellon, D. M., and Davidson, S. M. (2018). Comparison of small extracellular vesicles isolated from plasma by ultracentrifugation or size-exclusion chromatography: yield, purity and functional potential. *J. Extracell. Vesicles* 8:1560809. doi: 10.1080/20013078.2018.1560809
- Tang, Y., Han, L., Li, S., Zhang, X., Wang, J., Liu, Y., et al. (2023). Plasma GFAP in Parkinson's disease with cognitive impairment and its potential to predict conversion to dementia. *NPJ Parkinsons Dis.* 9:23. doi: 10.1038/s41531-023-00447-7
- Tian, C., Liu, G., Gao, L., Soltys, D., Pan, C., Stewart, T., et al. (2019). Erythrocytic alpha-synuclein as a potential biomarker for Parkinson's disease. *Transl. Neurodegener.* 8:15. doi: 10.1186/s40035-019-0155-y
- Tokuda, T., Qureshi, M. M., Ardah, M. T., Varghese, S., Shehab, S. A. S., Kasai, T., et al. (2010). Detection of elevated levels of alpha-synuclein oligomers in CSF from patients with Parkinson's disease. *Neurology* 75, 1766–1772. doi: 10.1212/WNL.0b013e3181fd613b
- Twohig, D., Rodriguez-Vieitez, E., Sando, S. B., Berge, G., Lauridsen, C., Oksengård, A. R., et al. (2018). The relevance of cerebrospinal fluid alpha-synuclein levels to sporadic and familial Alzheimer's disease. *Acta Neuropathol. Commun.* 6:130. doi: 10.1186/s40478-018-0624-z
- Usenko, T. S., Nikolaev, M. A., Miliukhina, I. V., Bezrukova, A. I., Senkevich, K. A., Gomzyakova, N. A., et al. (2020). Plasma cytokine profile in synucleinopathies with dementia. *J. Clin. Neurosci.* 78, 323–326. doi: 10.1016/j.jocn.2020.04.058
- Vallélunga, A., Ragusa, M., Di Mauro, S., Iannitti, T., Puzzo, L., Giunta, M. L., et al. (2014). Identification of circulating microRNAs for the differential diagnosis of Parkinson's disease and multiple system atrophy. *Front. Cell. Neurosci.* 8:156. doi: 10.3389/fncel.2014.00156
- van Steenoven, I., Aarsland, D., Weintraub, D., Londos, E., Blanc, F., van der Flier, W. M., et al. (2016). Cerebrospinal fluid alzheimer's disease biomarkers across the spectrum of Lewy body diseases: results from a large multicenter cohort. *J. Alzheimers. Dis.* 54, 287–295. doi: 10.3233/JAD-160322
- van Steenoven, I., Majbour, N. K., Vaikath, N. N., Berendse, H. W., van der Flier, W. M., van de Berg, W. D. J., et al. (2018). Alpha-Synuclein species as potential cerebrospinal fluid biomarkers for dementia with Lewy bodies. *Mov. Disord.* 33, 1724–1733. doi: 10.1002/mds.111
- van Wamelen, D. J., Taddei, R. N., Calvano, A., Titova, N., Leta, V., Shtuchniy, I., et al. (2020). Serum uric acid levels and non-motor symptoms in Parkinson's disease. *J. Parkinsons Dis.* 10, 1003–1010. doi: 10.3233/JPD-201988
- Veerman, R. E., Teeuwen, L., Czarnewski, P., Güclüler Akpınar, G., Sandberg, A., et al. (2021). Molecular evaluation of five different isolation methods for extracellular vesicles reveals different clinical applicability and subcellular origin. *J. Extracell. Vesicles* 10:e12128. doi: 10.1002/jev2.12128
- Vesely, B., Dufek, M., Thon, V., Brozman, M., Királová, S., Halászová, T., et al. (2018). Interleukin 6 and complement serum level study in Parkinson's disease. *J. Neural. Transm.* 125, 875–881. doi: 10.1007/s00702-018-1857-5
- Vesely, B., Koritakova, E., Bohnen, N. I., Vízslayova, D., Kiralova, S., Valkovič, P., et al. (2019). The contribution of cerebrovascular risk factors, metabolic and inflammatory changes to cognitive decline in Parkinson's disease: preliminary observations. *J. Neural. Transm.* 126, 1303–1312. doi: 10.1007/s00702-019-02043-7
- Villar-Menéndez, I., Porta, S., Buira, S. P., Pereira-Veiga, T., Díaz-Sánchez, S., Albasanz, J. L., et al. (2014). Increased striatal adenosine A2A receptor levels is an early event in Parkinson's disease-related pathology and it is potentially regulated by miR-34b. *Neurobiol. Dis.* 69, 206–214. doi: 10.1016/j.nbd.2014.05.030
- Vivacqua, G., Latorre, A., Suppa, A., Nardi, M., Pietracupa, S., Mancinelli, R., et al. (2016). Abnormal salivary total and oligomeric alpha-synuclein in Parkinson's disease. *PLoS ONE* 11:e0151156. doi: 10.1371/journal.pone.0151156
- Vivacqua, G., Suppa, A., Mancinelli, R., Belvisi, D., Fabbri, A., Costanzo, M., et al. (2019). Salivary alpha-synuclein in the diagnosis of Parkinson's disease and progressive supranuclear palsy. *Parkinsonism Relat. Disord.* 63, 143–148. doi: 10.1016/j.parkreldis.2019.02.014
- Vranová, H. P., Hényková, E., Kaiserová, M., Menšíková, K., Vašík, M., Mareš, J., et al. (2014). Tau protein, beta-amyloid1–42 and clusterin CSF levels in the differential diagnosis of Parkinsonian syndrome with dementia. *J. Neurol. Sci.* 343, 120–124. doi: 10.1016/j.jns.2014.05.052
- Wang, H., Atik, A., Stewart, T., Gingham, C., Aro, P., Kerr, K. F., et al. (2018). Plasma alpha-synuclein and cognitive impairment in the parkinson's associated risk syndrome: a pilot study. *Neurobiol. Dis.* 116, 53–59. doi: 10.1016/j.nbd.2018.04.015
- Wang, S., Liu, Z., Ye, T., Mabrouk, O. S., Maltbie, T., Aasly, J., et al. (2017). Elevated LRRK2 autophosphorylation in brain-derived and peripheral exosomes in LRRK2 mutation carriers. *Acta Neuropathol. Commun.* 5:86. doi: 10.1186/s40478-017-0492-y
- Wang, X., Yu, S., Li, F., and Feng, T. (2015). Detection of alpha-synuclein oligomers in red blood cells as a potential biomarker of Parkinson's disease. *Neurosci. Lett.* 599, 115–119. doi: 10.1016/j.neulet.2015.05.030
- Wang, Y., Hu, J., Chen, X., Wang, S., Zhang, C., Hu, J., et al. (2022). Real-time quaking-induced conversion assay is accurate for Lewy body diseases: a meta-analysis. *Neurol. Sci.* 43, 4125–4132. doi: 10.1007/s10072-022-06014-x
- Wang, Y., Shi, M., Chung, K. A., Zabetian, C. P., Leverenz, J. B., Berg, D. et al. (2012). Phosphorylated alpha-synuclein in Parkinson's disease. *Sci. Transl. Med.* 4:121ra20. doi: 10.1126/scitranslmed.3002566
- Wang, Z., Gililand, T., Kim, H. J., Garasimenko, M., Sajewski, K., et al. (2024). A minimally invasive biomarker for sensitive and accurate diagnosis of Parkinson's disease. *Acta Neuropathol. Commun.* 12:167. doi: 10.1186/s40478-024-01873-1
- Welsh, J. A., Goberdhan, D. C. I., O'Driscoll, L., Buzas, E. I., Blenkiron, C., Bussolati, B., et al. (2024). Minimal information for studies of extracellular vesicles (MISEV2023): from basic to advanced approaches. *J. Extracell. Vesicles* 13:e12404. doi: 10.1002/jev2.12404
- Wennstrom, M., Surova, Y., Hall, S., Nilsson, C., Minthon, L., Hansson, O. et al. (2015). The inflammatory marker YKL-40 is elevated in cerebrospinal fluid from patients with Alzheimer's but not Parkinson's disease or dementia with Lewy bodies. *PLoS ONE* 10:e0135458. doi: 10.1371/journal.pone.0135458
- White, A. J., Wijeyekoon, R. S., Scott, K. M., Gunawardana, N. P., Hayat, S., Solim, I. H., et al. (2018). The peripheral inflammatory response to alpha-synuclein and endotoxin in Parkinson's disease. *Front. Neurol.* 9:946. doi: 10.3389/fneur.2018.00946
- Williams, S. M., Schulz, P., and Sierks, M. R. (2016). Oligomeric alpha-synuclein and beta-amyloid variants as potential biomarkers for Parkinson's and Alzheimer's diseases. *Eur. J. Neurosci.* 43, 3–16. doi: 10.1111/ejn.13056
- Xylaki, M., Chopra, A., Weber, S., Bartl, M., Outeiro, T. F., and Mollenhauer, B. (2023). Extracellular vesicles for the diagnosis of parkinson's disease: systematic review and meta-analysis. *Mov. Disord.* 38, 1585–1597. doi: 10.1002/mds.29497
- Yan, S., Jiang, C., Janzen, A., Barber, T. R., Seger, A., Sommerauer, M., et al. (2024). Neuronally derived extracellular vesicle alpha-synuclein as a serum biomarker for individuals at risk of developing Parkinson disease. *JAMA Neurol.* 81, 59–68. doi: 10.1001/jamaneurol.2023.4398
- Yanamandra, K., Gruden, M. A., Casate, V., Meskys, R., Forsgren, L., and Morozova-Roche, L. A. (2011). alpha-Synuclein reactive antibodies as diagnostic biomarkers in blood sera of Parkinson's disease patients. *PLoS ONE* 6:e18513. doi: 10.1371/journal.pone.0018513
- Yilmaz, R., Straßfeld, A. P., Bernard, A., Schulte, C., van den Heuvel, L., et al. (2018). Serum inflammatory profile for the discrimination of clinical subtypes in Parkinson's disease. *Front. Neurol.* 9:1123. doi: 10.3389/fneur.2018.01123
- Youssef, P., Hughes, L., Kim, W. S., Glenda M. Halliday, Simon J. G., et al. (2013). Evaluation of plasma levels of NFL, GFAP, UCHL1 and tau as Parkinson's disease biomarkers using multiplex single molecule counting. *Sci. Rep.* 13:5217. doi: 10.1038/s41598-023-32480-0
- Youssef, P., Kim, W. S., Halliday, G. M., Lewis, S. J. G., and Dzamko, N. (2021). Comparison of different platform immunoassays for the measurement of plasma alpha-synuclein in Parkinson's disease patients. *J. Parkinsons. Dis.* 11:1761. doi: 10.3233/JPD-212694
- Zanganeh, S., Arias, G., Cone, A., Yuan, R., and Dittmer, D. P. (2026). Protocol for large-scale, high-yield, high-purity extracellular vesicle purification from human plasma. *STAR Protoc.* 7:104428. doi: 10.1016/j.xpro.2026.104428
- Zhao, Y., and Yang, G. F. (2021). Potential of extracellular vesicles in the Parkinson's disease-pathological mediators and biomarkers. *Neurochem. Int.* 144:104974. doi: 10.1016/j.neuint.2021.104974
- Zhao, Z. H., Chen, Z. T., Zhou, R. L., Zhang, X., Ye, Q. Y., and Wang, Y. Z. (2019). Increased DJ-1 and alpha-synuclein in plasma neural-derived exosomes as potential markers for Parkinson's disease. *Front. Aging Neurosci.* 10:438. doi: 10.3389/fnagi.2018.00438

Zheng, H., Xie, Z., Zhang, X., Mao, J., Wang, M., Wei, S., et al. (2021). Investigation of alpha-synuclein species in plasma exosomes and the oligomeric and phosphorylated alpha-synuclein as potential peripheral biomarker of Parkinson's disease. *Neuroscience* 469, 79–90. doi: 10.1016/j.neuroscience.2021.06.033

Zhou, B., Wen, M., Yu, W. F., Zhang, C. L., and Jiao, L. (2015). The diagnostic and differential diagnosis utility of cerebrospinal fluid alpha-synuclein levels in Parkinson's disease: a meta-analysis. *Parkinson Dis.* 2015:567386. doi: 10.1155/2015/567386

Zimmerman, M., and Brockman, K. (2022). Blood and cerebrospinal fluid biomarkers of inflammation in Parkinson's disease. *J. Parkinson Dis.* 12, S183–S200. doi: 10.3233/JPD-223277

Zubelzu, M., Morera-Herreras, T., Irastorza, G., Gómez-Esteban, J. C., and Murueta-Goyena, A. (2022). Plasma and serum alpha-synuclein as a biomarker in parkinson's disease: a meta-analysis. *Parkinsonism Relat. Disord.* 99, 107–115. doi: 10.1016/j.parkreldis.2022.06.001