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Revolutionary biomarkers: Transforming the Future of Parkinsonism Diagnosis

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ABSTRACT

Introduction: After Alzheimer's disease, Parkinson's disease (PD), which is distinguished by gradual motor impairment, is the subsequent prominent neurodegenerative movement disease. Differentiating PD from other Parkinsonian disorders is challenging due to overlapping symptoms.

Objective: This review aims to provide a comprehensive overview of current developments in the search for biomarkers for Parkinson's disease (PD), with a focus on their utility in differentiating PD from other Parkinsonian syndromes.

Methods: A thorough analysis of existing literature was conducted also explores relevant research articles, clinical trials, and meta-analyses to discuss their applications in early detection, differential diagnosis, and monitoring disease progression.

Results: α-Synuclein Seed Amplification Assays (SAAs) in CSF show great promise for early and accurate PD diagnosis due to their high sensitivity and specificity. GFAP, while less specific, can be valuable for monitoring neurodegeneration severity. CSF levels of Aβ42, p-tau, and t-tau can help predict cognitive impairment in PD, particularly in differentiating PDD from PDMCI. YKL-40 can differentiate as well as activation of macrophages and microglia. Integrating non-motor symptom assessments with objective biomarker measurements may improve the accuracy of early PD diagnosis.

Conclusion: CSF biomarkers, particularly α-Synuclein SAAs, hold significant potential for improving the diagnosis and management of PD. While individual biomarkers have limitations, combining them with clinical assessments and auxiliary methods can enhance diagnostic accuracy. Further research, including longitudinal studies and validation in diverse cohorts, is needed to fully realize the clinical utility of these biomarkers in predicting treatment response and understanding the underlying pathophysiology of PD.

Keywords: *Parkinson's disease, neurodegenerative disease, biomarker, diagnosis.*

1. INTRODUCTION

Over a million people, usually older, suffer with PD. This neurodegenerative disorder characterized by a progressive and intensifying bradykinesia, stiffness, and resting tremors that ultimately results in a loss of movement [1]. Differentiating PD from other Parkinsonian disorders because of its symptoms' similarities to those of other conditions, such as dementia with Lewy bodies (DLB), progressive supranuclear palsy, multiple system atropy (MSA) and essential tremors.

Biomarkers stands for biological markers, refers to quantifiable substances or indicators that may be objectively recognized and assessed to offer insights into pharmacological, pathological, or physiological processes. Biomarkers play a crucial role in diagnosing diseases, monitoring their progression, assessing responses to treatments, and identifying individuals at risk for certain conditions. They offer the customization of therapy according to individual features and offer significant understanding regarding the fundamental causes of diseases.

A biomarker for Parkinson disease could be beneficial for: -

a) **Early Detection and Diagnosis:** Biomarkers can facilitate the early detection of PD before significant symptoms manifest. Early diagnosis is crucial for timely intervention and the implementation of appropriate treatment strategies. Early identification of at-risk individuals may allow for preventive measures or closer monitoring.

b) **Monitoring Disease Progression:** Biomarkers enable the tracking of disease progression over time. This is essential for understanding how the condition evolves and for assessing the effectiveness of therapeutic interventions.

c) **Evaluation and Designing of Clinical Trial:** Biomarkers are essential in clinical trials for the clinical development of new drugs and treatments. They can be used to select participants, monitor treatment response, and assess the impact of experimental therapies on the underlying disease processes.

d) **Personalized Medicine:** Biomarkers contribute to the concept of personalized medicine by allowing for the tailoring of treatments based on an individual's specific characteristics and the molecular profile of their disease.

e) **Understanding Disease Mechanisms:** Biomarkers provide insights into the underlying biological mechanisms of PD progression. This knowledge is valuable for researchers and clinicians in developing targeted therapies and advancing the overall understanding of the disease.

Minimizing Diagnostic Errors: Since Parkinson's disease shares symptoms with other neurological disorders (such as dementia with Lewy bodies (DLB), progressive supranuclear palsy, multiple system atropy (MSA), a reliable biomarker can minimizes the probability of misdiagnosis, ensuring that individuals receive appropriate and timely care.

How biomarkers evolve the detection and treatment procedure: -

In order to effectively utilize biomarkers for PD, it is crucial to understand precisely what they are measuring and the extent of the information they can offer in detection of the disease and what are the limitation or the informations which they cannot provide. There is a distinction between the underlying disease process, which may involve events such as Lewy body formation, neuronal loss, and dopamine depletion, and the various clinical presentations that result from this process.

The obstacle in PD lies in the weak correlation between clinical symptoms and pathology. This means that knowing a patient's pathology does not reliably predict their clinical presentation (Figure1), and conversely, understanding their symptoms does not accurately reflect their pathology (Figure 2). For instance, a patient's symptoms may vary greatly throughout the day, while their pathological condition remains constant. Moreover, about 10% of individuals aged 60 or above have Lewy bodies in their brains without apparent cause, yet only a small percentage of these individuals ever exhibit symptoms [2, 3]. Additionally, our capacity to predict pathology from clinical symptoms is limited.

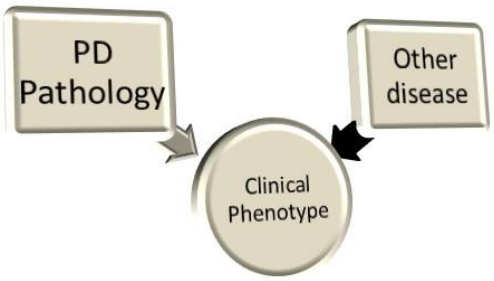

Figure 1: Similarity of PD with other Parkinsonian disease[4]

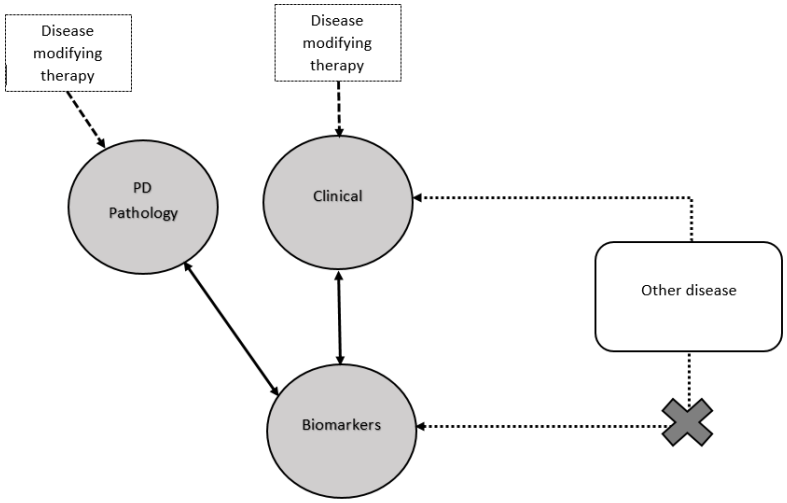

Figure 2: Personalized and Precised therapies in association with Biomarkers [4]

Consequently, a biomarker aimed at detecting pathology may not necessarily yield clinical insights, and vice versa. However, in practice, markers intended to provide information about pathology can also offer some insights into clinical symptoms through correlation. For instance, the use of 11C-WAY100635 PET imaging of serotonergic activity not only shows a decline in signaling from the median raphe nucleus but also aligns with the presence of rest tremors [5]. It is crucial to understand the initial purpose of the biomarker—in this instance, PET imaging—which was to detect pathological changes, and to recognize the supplementary insights gained through its correlation with clinical symptoms, such as rest tremor. In this context, the PET scan itself is not a direct biomarker for rest tremor, and the correlation observed might not hold in a different group of individuals.

This study provides a thorough analysis of current developments in the hunt for biomarkers for PD, with an emphasis on differentiating PD from similar Parkinsonian conditions. In this review biomarkers are categorized based on the source of sample collection and method of diagnosis (Figure 3):

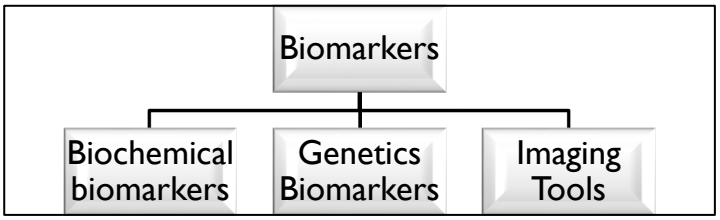

Figure 3: Classification of Biomarkers on the basis of source of Sample collection and method of diagnosis

Biochemical biomarkers: Understanding the pathophysiology of the disease is the most appropriate framework for the synthesis of biochemical markers for early identification and progression of Parkinson's disease. The pathogenetic processes of inflammation, oxidative stress, mitochondrial dysfunction, and protein accumulation, aggregation, and propagation are all thought to be significant [6, 7]. Biochemical biomarkers are characterized on the basis of sample acquisition (Figure 4):

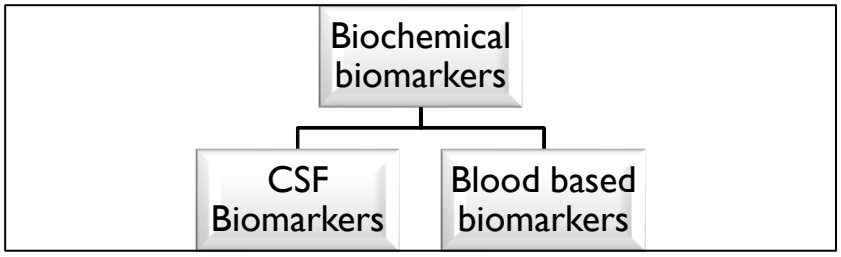

Figure 4: Classification of Biochemical biomarkers on the basis of source of Sample aquisition

CSF = Cerebrospinal fluid

Cerebrospinal Fluid (CSF) Biomarkers:

Analysis of cerebrospinal fluid is widely used as a key indicator for the diagnosis of various disorders affecting nervous system. CSF is preferred as a biomarker source in research over blood because examining CSF offers a direct glimpse into the CNS extracellular space, which allows the identification of physiological changes that occurs within CNS [8]. In PD, Blood-Brain Barrier (BBB) is disrupted. Consequently, analysis of cerebrospinal fluid holds promise for revealing biomarkers linked to PD [9]. Changes in the concentrations or characteristics of these biomarkers in the CSF can offer insights into the underlying pathology, aid in the diagnosis, and evaluate disease development or how well PD and other neurological disorders are being treated. Key CSF biomarkers mentioned in Figure 5:

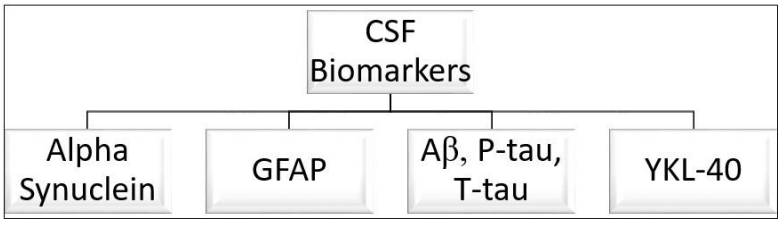

Figure 5: Key CSF biomarkers crucial in distinguishing PD from other parkinsonian disease

CSF = Cerebrospinal fluid, Aβ = Beta amyloid, P-tau = Phosphorylated tau, T-tau = Total tau, YKL-40 = chitinase-3-like protein 1.

α-Synuclein (a-Syn): In 1912, Friedrich Lewy discovered and characterized the protein aggregates as Lewy bodies within neurons [10]. It was discovered that misfolded and aggregated alpha-synuclein was responsible for the majority of lewy bodies [Figure 6]. The abnormal deposition of α-syn within neurons is a characteristic of Lewy bodies in patients with PD, and this is the key CSF biomarker for the disease. Elevated α-syn levels in plasma were discovered in PD patients, and these levels were linked to prolonged duration of the disease [11].

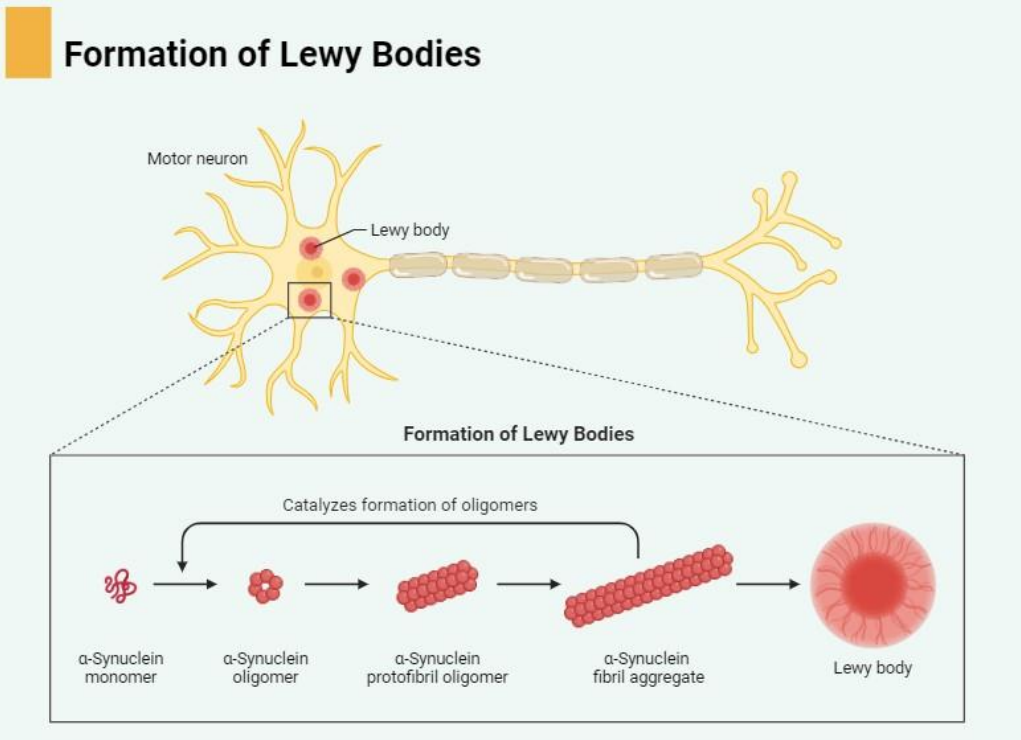

Figure 6: Formation of Lewy Bodies from α-synuclein monomer

PD and **DLB** both have lewy bodies [12]. As an alternative to conventional CSF evaluation, Seed Amplification Assays (SAAs) of α-syn in CSF investigated recently. This assay was validated in April 2023 and received an FDA "Letter of Support" in September 2024, encouraging its use in clinical trials and drug development. These techniques discovered trace levels of disease-specific protein aggregates by detecting the seeding capabilities of proteins [13- 15]. A research with 172 individuals, **SAA** was reported to have a 98% specificity and a 95.3% sensitivity for identifying α-syn in alpha-synucleinopathies in relationship with Lewy bodies [16].

A recent investigation by von Euler Chelpin *et al.* (2020), patients with PD have higher amounts of α-syn protofibrils in their CSF, however there is some overlap with those of elderly people who do not exhibit any symptoms. A group of 49 PD patients, 12 people with **CBD**, 22 people with **PSP**, and 33 controls who sought assistance at a memory clinic but did not show any signs of AD were included in the investigation. The researchers achieved a specificity of 67.7% and a sensitivity of 62.8% by Single molecule array (Simoa) method to accurately predict PD based on alpha-synuclein protofibril levels [17].

SAA of α-syn in CSF samples is a viable method for early PD diagnosis, according to significant research by Siderowf *et al.* (2023). 1123 people from eight countries participated in this cross-sectional investigation. Healthy controls, **PD** patients, prodromal patients, those with **Parkinsonism but negative DAT** scans, and asymptomatic carriers of PD-related genes were the groups into which the participants were divided. Results demonstrated that the specificity for identifying PD in healthy controls was 96.3%, while the sensitivity for identifying PD in patients was 88% [18].

It could be particularly beneficial to express data as an oligomeric to total alpha-synuclein ratio. According to one analysis, this ratio has an AUC of 0.948, a specificity of 90.6% and a sensitivity of 89.3% for the detection of PD [19]. The use of the oligomeric to total alpha-synuclein ratio is also supported by two other research [20, 21].

Considering that the non-motor symptom's specificity alone is typically inadequate for early PD diagnosis, integrating additional objective measures and auxiliary methods with non-motor symptom results could improve the predictive accuracy of Parkinson's disease biomarkers.

(GFAP) Glial fibrillary acidic protein: - The intermediate filaments GFAP and vimentin are expressed by astrocytes, the most prevalent cell type in the CNS of human [22]. GFAP, a vital component of white matter architecture, BBB integrity, and myelination, is the predominant intermediate filament in astrocytes [23]. It also helps to preserve the motility and shape of astrocytic processes [24].

GFAP has been found to have no extra-cerebral sources, and healthy people have very low blood levels of the protein. It is believed that situations like BBB disruption and loss of astrocytic structural integrity from necrosis or mechanical disruption cause GFAP to be released from brain tissue into the bloodstream. Additionally, GFAP is an essential intermediate filament protein that supports the BBB and nearby neurons while preserving glial shape and mechanical strength [25].

Research indicates that GFAP and the breakdown products of GFAP (GFAP-BDPs) are valuable biofluid-based biomarkers for neurological diseases including Parkinson's disease. In the interstitial/extracellular fluid, GFAP-BDPs and to some extent, full-length GFAP are released as a result of astrocytic damage. These proteins can then follow the flow of CSF and diffuse through the blood-brain barrier, or they can enter the bloodstream directly through venous drainage. The brain-specific nature and high expression of GFAP make it a valuable biomarker [26, 27].

Therefore, astrocytic damage is indicated by elevated levels of GFAP and its breakdown products, which suggests neurodegenerative disease. The diagnostic sensitivity of GFAP is restricted due to increased CSF, even if it signifies an aberrant disease process. GFAP levels have also been found in various neurodegenerative conditions like DLB, frontotemporal dementia, Alzheimer's disease and Creutzfeldt-Jakob disease [28- 30].

However, GFAP may be helpful in monitoring the degree of neurological degeneration along with the course of PD [31].

In conclusion, GFAP and GFAP-BDPs serve as valuable biomarkers for neurological conditions, including Parkinson's disease (PD), as they indicate astrocytic damage and suggest the presence of neurodegenerative processes. Although increased GFAP levels in the CSF are indicative of an aberrant disease process, the specificity of GFAP as a diagnostic marker is limited due to its elevation in various other neurodegenerative diseases as well.

Despite this limitation, GFAP and its breakdown products could be instrumental in monitoring the progression of PD and the extent of neurological degeneration, providing information on how the condition interferes with the central nervous system.

Beta amyloid (Aβ), P-tau and T-tau: - The diagnosis at an initial phase of AD depends on a CSF profile, which is defined by elevated t-tau, p-tau 181, and reduced Aβ 1-42. P-tau, t-tau and Aβ42 levels are important indicators of cognitive impairment in Parkinson's disease (PDCI), as per wide range of studies.

The two phenotypes of PDCI are dementia (PDD) and mild cognitive impairment (PDMCI) are identified [32]. PDMCI is commonly seen as a transitional stage between PDD and PD with normal cognition (PDNC). PD is often made worse by dementia that affects about 10% of people annually. Lewy body pathology is the main contributor to PDD, along with evidence suggesting a additional effect with Aβ [33].

According to a recent meta-analysis by Hu *et al.* (2017) that included 16 cohort studies, patients with PDCI had notably reduced CSF Aβ42 levels than those with PDNC, with PDD patients showing the most noticeable reduction. Additionally, the study discovered elevated levels of p-tau and t-tau in CSF related with **PDD** patients than **PDNC** patients, indicating that PDD is more closely linked to CSF markers (Aβ, p-tau and t-tau) than with PDMCI [34].

Nebizadeh *et al.* implemented partial correlation models that were adjusted for sex, age and duration of education during a follow-up period of 24-months in a longitudinal and cross-sectional study that looked at the relationship in dopamine uptake and markers of CSF. According to this study, Aβ pathology may occur prior to dopaminergic deterioration in the striatal nuclei, especially the left caudate, which could then cause cognitive impairment in PD patients, which involved 187 healthy controls and 413 individuals with initial phase of PD [35].

The longitudinal effect of baseline cerebrospinal fluid (CSF) biomarkers on total and regional brain volume and thickness was assessed by Alberto *et al.* using linear mixed models in a cross-sectional investigation assessing the relationship between Aβ42, p-tau and t-tau levels and brain volume in PD patients. For cross-sectional investigation at baseline along with year 2, they also used linear regression. The researchers concluded that there was **no** meaningful **correlation** between the baseline values of the biomarkers and the 4-year changes in the volume of the brain. But according to the cross-sectional investigation, PD patients' brain volumes are smaller when their levels of soluble Aβ are reduced [36].

In conclusion, the CSF profile characterized by changes in Aβ42, p-tau and t-tau levels which is not only crucial for the diagnosis of AD at an early stage but also for understanding and predicting cognitive impairment in PD. These biomarkers are more closely associated with **PDD** than with **PDMCI** and may indicate a pathological process that begins before the onset of significant dopaminergic neuron loss. This could provide information about the mechanisms underlying cognitive decline in PD along with opportunities for early intervention.

YKL-40: - A glycoprotein of 40 kDa that is a member of the family mammalian chitinase-like protein, human cartilage glycoprotein-39, also known as chitinase-3-like protein 1 (CHI3L1/YKL-40) and serves as a diagnostic tool for the differentiation as well as activation of macrophages and microglia [37]. YKL-40 is expressed by astrocytes and is elevated in numerous degenerative neurological disorders including Alzheimer's disease, amyotrophic lateral sclerosis, and frontotemporal lobar degeneration [38, 39].

According to a research in 2019 by Morenas-Rodríguez *et al.* that investigated the CSF profiles of 207 individuals, discovered that CSF profile of DLB patients with AD (Ratio >0.52 of t-tau/ Aβ 1-42) had much higher CSF YKL-40 levels than those with a common AD ($p = 0.04$). YKL-40 may not be helpful for early DLB detection, as this study failed to discover an elevation in CSF YKL-40 level across the prodromal stages of DLB. However, elevated levels of CSF YKL-40 in DLB individuals with an AD suggests that AD-related neurodegeneration, not DLB pathology, is the cause of the elevation. Thus, YKL-40 may be beneficial in assessing DLB patients who have concurrent AD pathology, but it isn't recommended as a potential CSF biomarker for DLB in general [40].

Fathi, M. H. and Anwar, M. M. (2023) recently conducted a rodent study in which the animals were categorized into three distinct groups: Early LPS-induced PD (14 days) and Control. According to the study, PD-induced rats' brain tissue and CSF had higher levels of YKL-40 expression, which was correlated with the release of inflammatory cytokines [41].

In a cross-sectional investigation, Gevezova *et al.* (2023) explored the relationship between PD mitochondrial dysfunction and YKL-40. This study demonstrated that eighteen newly diagnosed PD patients had considerably higher YKL-40 levels than seven age-matched healthy controls. These levels showed a correlation with ATP generation and basal respiration, indicating a connection among mitochondrial function and YKL-40. The findings propose a potential role for YKL-40 as a biomarker for monitoring the clinical course of PD, given its association with bioenergetic parameters and inflammation. The authors suggest that mitochondrial dysfunction, linked to neuronal loss and oxidative stress, may occur before the onset of sign and symptoms of PD, highlighting the importance of identifying biomarkers like YKL-40 for early detection and personalized therapy [42].

Table 1. Key CSF biomarkers in PD

Biomarker	Variation	Conclusion	References
Alpha-Synuclein	**Decrease**	**Alpha synuclein demonstrates a higher specificity and sensitivity in predicting the alpha synucleopathy and reduces the errors in misdiagnosis in patients (↓PD, ↓MSA, ↑CBD, ↑PSP)**	**[11], [12], [13], [14], [15], [16], [17], [19], [20], [21]**
GFAP	**Increase**	**Increased level of GFAP and its breakdown products is remarkable marker for asttrocytic injury.**	**[25], [26], [27], [28], [29], [30], [31]**
Amyloid beta (1-42)	**Decrease**	**Synergistic effect,** **Decreased level in PDCI compared to PDNC.**	**[21], [34], [36]**
P-tau, T-tau	**Increase**	**Major constituents in cognitive impairment and crucial for early diagnosis before the neuronal loss.**	**[21], [34]**

YKL-40	**Increase**	**Elevated level linked to oxidative stress and mitochondrial damage seen prior to PD symptoms.**	**[40], [41], [42]**

PD = Parkinson disease, MSA = Multiple System Atropy, CBD = Corticobasal Desgeneration, PSP = Progressive Supranuclear Palsy, GFAP = Glial fibrillary acidic protein, PDCI = Cognitive Impairment in Parkinson's disease, PDNC = Parkinson disease with normal cognition, P-tau = Phosphorylated tau, T-tau = Total tau, YKL-40 = chitinase-3-like protein 1.

Blood based biomarkers: - Even if there are authentic biomarkers for PD diagnosis, such as imaging or CSF biomarkers, the primary objective is to identify an effective blood-based biomarker. This might improve PD diagnosis, evaluate therapeutic responses, assess disease progression, and identify PD subtypes without requiring the specialized expertise and costly equipment needed for imaging or the invasiveness of a lumbar puncture. Relatively simple to obtain, blood biomarkers have the potential to be very helpful if they fulfill the requirements for research and clinical use. Numerous potential blood based biomarkers could aid in diagnosing **PD** or differentiating between various **Parkinson's plus syndromes**. Furthermore, among patients who have already been diagnosed with PD, certain biomarkers may be able to predict symptom's severity or cognitive deterioration [43]. Key Blood based markers mentioned in Figure 7:

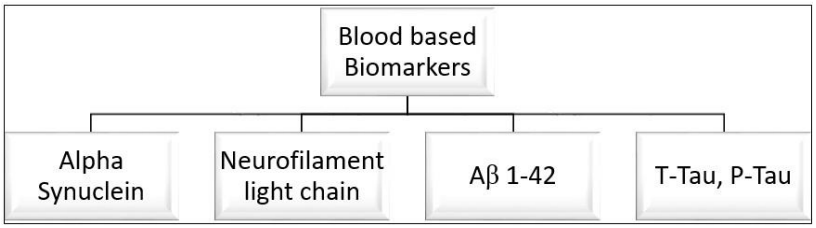

Figure 7: Key Blood based biomarkers crucial in distinguishing PD from other parkinsonian disease

Aβ = Beta amyloid, T-tau = Total tau, P-tau = Phosphorylated tau.

Alpha synuclein: - Red blood cells, or erythrocytes, have the highest concentrations of α-Syn, a compact protein made up of 140 amino acids, which can be detected in blood [44]. The exploration of α-Syn as a notable indicator in peripheral samples began in 2003, when it was serendipitously identified in plasma by David Allsop's research team [45]. This finding broadened the study of alpha-synuclein to examine its possible use in serum in addition to its well-established function as a CSF biomarker. α-syn is thought to be an excellent choice for a sensitive and specific blood-based biomarker in the diagnosing the PD and to evaluate the development of diseases due to its strong correlation with its pathology.

Lewy neuritis and Lewy bodies are formed when alpha-synuclein accumulates within neurons in **DLB** and **PD**. Alternatively, it is primarily seen among oligodendrocytes in MSA as glial cytoplasmic inclusions (GCIs) [46-48]. Despite the unique symptoms and pathophysiological mechanisms of these synucleinopathies, early-stage diagnoses are frequently inaccurate due to symptom overlap with other synucleinopathies, atypical parkinsonian tauopathies, spinocerebellar ataxias, and various dementias [49-51]. In PD, the accuracy of the diagnosis roughly 80%, which declines for newly diagnosed individuals [52, 53]. In rarer synucleinopathies, the misdiagnosis rates are much higher [54, 55].

Comprehensive meta-analysis of over 30 researches showed that, although there was significant variation across the studies, total blood α-Syn levels were actually higher among PD patients than in controls. With a confidence interval spanning from 0.27 to 1.42, the standardized mean difference for total α-Syn was 0.85 (dimensionless because of the meta-analysis approach). Data from 1838 controls and 2683 PD patients were included in this analysis [56].

In a 2021 study by Suman Dutta and colleagues, two separate cohorts were examined: a discovery cohort and a validation cohort. The researchers collected serum samples from 50 PD patients, 51 healthy controls, and 30 MSA patients. They found that when comparing **MSA** patients to **PD** patients, the concentration of alpha-synuclein in exosomes was considerably greater in MSA patients and significantly lower in healthy controls. Utilizing data from the discovery cohort, a multinomial logistic model was created and then applied to the validation cohort. With AUC of 0.902, this model—which incorporated the α-Syn concentration ratio, total exosome concentration, and the alpha-synuclein concentration itself—showed high specificity (86.0%) and sensitivity (89.8%) in distinguishing between MSA and PD [57].

According to numerous studies on α-Syn levels in blood serum, PD patients' α-syn levels were either higher [57- 59], lower [60, 61], or significantly different or not different from those of healthy individuals [62, 63].

Chen-Chih Chung's 2021 cross-sectional study comprised 162 participants, 46 of whom were healthy controls and 116 of whom were PD patients. The results showed significant negative correlation of plasma EV α-syn levels and the degree of akinetic-rigidity, with PD patients having considerably decreased levels than healthy individuals. However, there was no association with cognitive function, age, or the period of the disease. According to the study, plasma EV α-syn could be used as a biomarker for classifying and diagnosis of PD, especially for the akinetic-rigidity subtype. The limitations of the study are also discussed, such as the evaluation of total α-synuclein rather than its toxic variants and the utilization of total plasma EVs rather than neuron-derived EVs [64].

A recent study by Joseph Blommer (2023) included plasma samples from 273 participants, including sex-matched controls and PD patients who had and hadn't cognitive impairment. They found that PD patients, especially those with cognitive impairment, had lower levels of α-Synuclein than controls. PD patients, particularly those with cognitive impairment, have greater levels of phosphorylated tau (T181) than controls. PD patients, especially those having cognitive deficits and more severe motor symptoms, exhibit lowered levels of tyrosine-phosphorylated insulin receptor substrate-1 (pY-IRS-1). The study suggests that both α-synuclein and tau pathologies, along with impaired insulin signaling, are involved in PD with cognitive impairment [61].

Despite these promising findings, research on alpha-synuclein levels in serum or plasma has yielded inconsistent results, with some studies showing increases, decreases, or no significant differences among PD patients and healthy individuals. This variability underscores the necessity for further investigation to completely comprehend the function of α-syn as a key indicator of PD and other synucleinopathies, as well as to develop reliable and standardized assays for its measurement in peripheral blood samples.

Neurofilament light chain: - The protein known as neurofilament light chain (NfL), which is present in the cytoplasm of neurons, is crucial for sustaining the structural strength of axons and promoting the conduction of nerve impulses. Neurofilament heavy (110 kDA) and medium (100 kDA) chain proteins are the other two subunits that make up neurofilaments [65, 66]. The extent of axonal injury in several neurological disorders such as inflammatory, traumatic, degenerative, and cerebrovascular diseases, is indicated by increased NfL levels in CSF and blood [67].

NfL levels naturally rise with age, necessitating the use of age-adjusted values. PD patients' cognitive loss was significantly predicted by levels of NFL among the top 5% for age, according to a recent study that examined data from two previous studies [68].

In a Taiwanese research, Hong's group validated the significance of adjusting for demographic characteristics including gender and age. This study differentiated a large Western cohort with a small Taiwanese cohort of PD patients and healthy individuals. The investigators compared the blood NfL levels of the large international, multi-center Parkinson's Progression Markers Initiative (PPMI) cohort with those of a domestic, single-centered PD cohort from Shuang Ho Hospital (SHH) in Taiwan. Despite the fact that the SHH-healthy controls' plasma NfL levels were initially greater than those of the PPMI group, especially in females, these disparities were abolished once certain demographic characteristics were taken into account. According to the findings, blood NfL levels and the likelihood of PD diagnosis were positively correlated in both cohorts, indicating that NfL could be a valuable biomarker for PD. However, the investigation emphasized the need to adjust for variables such as age and gender in biomarker studies to minimize bias and enhance the comparability of results across different cohorts [69].

NFL plasma levels were shown considerably greater in the PDD group than PDND group in the research by Lin *et al.* (2018). The study included normal healthy individuals, AD, PD, and amnesic MCI. According to the findings, the mean plasma NFL level was 16.4 ± 9.9 pg/ml in patients with PDND, 17.8 ± 6.4 pg/ml in controls, 23.3 ± 10.8 pg/ml in patients with PDD and 32.9 ± 25.5 pg/ml in patients with AD and MCI. Compared to female patients, plasma NFL levels were higher in male patients ($p = 0.03$, t-test). This age-related effect was seen in all subgroups, as plasma NFL levels increased with age. Even after controlling for gender, age, duration of education and status of APOE ε4 carrier, the plasma NFL levels of AD patients were significantly greater than those of PDND (all $p < 0.001$), MCI, PDD ($p = 0.047$) or HC. The plasma NFL levels of PDD patients were substantially greater than both healthy individuals and PDND. **MCI and PD** patients as well as **MCI and PDND** patients, had comparable levels of plasma NFL. Even after further adjustments levels of plasma NFL were greater in AD patients when compared with HC along with PDND [70].

A cross-sectional study conducted by Chen-Chih Chung in 2020 with 162 individuals, 46 of whom were healthy controls and 116 of whom were PD patients. The study revealed lack of statistically significance between controls and PD patient in plasma extracellular vesicle NfL levels. The degree of PD motor symptoms was found to be somewhat correlated with plasma extracellular vesicle NfL levels, with intensity of mild motor symptom being linked to ideal plasma EV NfL levels [71]. Levels of NfL shown to be elevated in a number of neurological disorders, particularly in **PD** and **AD**. These levels are also linked to cognitive decline and disease severity. However, the need for age and gender adjustment is crucial for accurate interpretation of NfL levels as a biomarker.

Table 2. Important Blood based biomarkers in PD

Biomarker	Variation	Conclusion	Reference
Alpha-Synuclein	Decrease	α-synuclein levels can be increased, decreased, or unchanged in PD patients compared to controls, and its concentration in plasma extracellular vesicles (EVs) has been associated with the severity of akinetic-rigidity symptoms.	[60], [61], [64]
	Increase		[56], [57], [72], [73], [74], [75], [76], [77], [78]
Neurofilament light chain (NFL)	Increase	NfL levels are associated with disease severity and cognitive impairment with the need to adjust covariates for accurate results.	[69], [70], [71]

Genetic biomarkers: - Genetic markers are essential for comprehending the risk and potential development of PD. These biomarkers encompass specific mutations and genetic variations that can signal an individual's susceptibility to PD. Key genetic biomarkers mentioned in Figure 8:

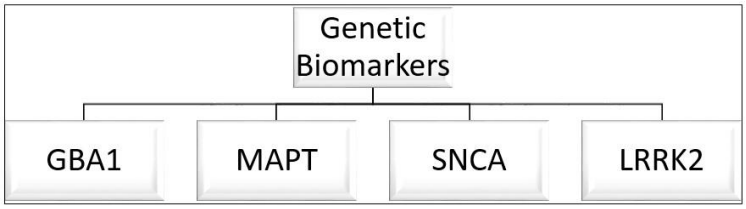

Figure 8: Key Genetic biomarkers crucial in distinguishing PD from other parkinsonian disease

GBA1 = Glucocerebrosidase, SNCA = *α-synuclein, LRRK2* = Leucine-rich repeat kinase 2

The two most significant genetic markers are mutations in the LRRK2 and α-synuclein (SNCA) genes. Autosomal dominant types of PD are linked to SNCA mutations, which include point mutations, duplications, and triplications. These mutations are characterized by high penetrance, indicating that individuals with these mutations have a substantial likelihood of developing the disease, although the onset age can vary considerably, from the mid-30s to the late 80s [79].

A large multi-national cohort study by Guella *et al.* (2016) included 1,492 PD patients, 922 DLB patients, and 971 healthy controls. The study identified two distinct association patterns for Parkinsonism and dementia symptoms linked to different regions of the SNCA gene. A specific haplotype in intron 4, characterized by an expanded TTTCn repeat, was found to be directly associated with PDD. When contrasted with healthy controls, this haplotype was substantially more common in **PDD** and **DLB** patients [80].

Another important genetic marker is the LRRK2 gene, which accounts for 1% to 2% of sporadic illnesses and 10% to 15% of familial cases in white populations. The G2019S mutation in LRRK2 is especially common in certain ethnic groups, such as Ashkenazi Jews and North African Arabs, where its prevalence can reach 30-40% in familial cases. However, the penetrance of this mutation is both age-dependent and incomplete, with estimates indicating that only 30-40% of carriers will develop PD over their lifetime [81].

Although genetic markers can help categorize patient groups and assist in epidemiological research, their effectiveness in predicting individual risk is limited. The variability in penetrance and expressivity means that having a genetic mutation does not ensure the development of PD, making these markers more valuable for understanding population-level risks rather than

individual outcomes [82].

In order to explore potential biomarkers linked with glucocerebrosidase (GCase) for GBA1-associated PD (GBA-PD), van Heijer *et al.* (2023) integrated data from five investigations into a cross-sectional research. The investigation evaluated the differences in glycosphingolipids (GSLs) among **idiopathic PD** (iPD), **GBA-PD** and healthy volunteers (HVs) in a variety of biological matrices (PBMCs, plasma and CSF). The results indicated that glucosylceramide can be accurately measured in plasma and peripheral blood mononuclear cells (PBMCs), suggesting its potential as a biomarker for GBA-PD. The study emphasized the importance of considering the biological matrix and cell type when measuring GSLs, as these factors can significantly affect the results [83].

A retrospective research by Tunold *et al.*, (2021) investigated the significance of genetic variables, particularly the MAPT H1 haplotype and the APOE ε4 allele, progression of dementia in patients with PD. The researchers observed that both genetic variations had a significant relationship with an earlier onset of dementia, with the APOE ε4 allele exhibiting a high connection with amyloid pathology, using a retrospective survival study of brain donors whose PD was neuropathologically confirmed. The findings emphasized how crucial these genetic markers are to comprehending the causes of **PDD** and offered possible uses for patient selection and risk stratification in clinical trials aimed at cognitive decline. Regardless of these findings, the authors outlined significant obstacles to verifying these associations in larger, longitudinal cohorts, including the need for additional research and the small sample size [84].

In summary, genetic markers, particularly alterations in the SNCA and LRRK2 genes, are vital for understanding the risk and progression of PD. While these markers can help classify patient groups and support epidemiological research, their predictive value for individual risk is limited due to variability in penetrance and expressivity. Furthermore, genetic variables such the MAPT H1 haplotype and the APOE ε4 allele have been found interlinked with an earlier development of dementia in PD patients, as well as possible biomarkers linked to GCase for GBA-PD. These results demonstrate the intricacy of PD and the necessity for deeper investigation to fully comprehend the hereditary components of the illness and its associated dementia.

Imaging tools: - In order to support observations in clinical studies, imaging biomarkers are being used more and more in the detection of PD. These biomarkers encompass a number of methods mentioned in Figure 9:

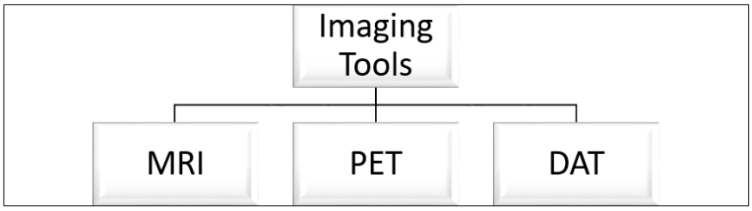

Figure 9: Key imaging biomarkers crucial in distinguishing PD from other parkinsonian disease

MRI = Magnetic Resonance Imaging, PET = Positron Emission Tomography, DAT = Dopamine Transporter

A non-surgical imaging method such as MRI produces highly refined visuals of the brain and other soft tissues. It is especially helpful in determining whether neuromelanin (NM) and iron content are present and intact in certain brain areas associated with PD, including the ventral tegmental area, locus coeruleus, and substantia nigra pars compacta (SNpc).

By offering important information on the integrity of neuromelanin and iron content in the brain, MRI assists in detecting and monitoring PD, facilitating early detection and differentiation from other neurodegenerative diseases [85].

Numerous requirements for useful markers of PD are met by 18-fluoro-dopa PET and other dopamine presynaptic markers, such as the vesicular monoamine transporter type 2 or DAT, which are detected by single photon emission tomography (SPECT). These markers reflect the deterioration of nigrostriatal dopamine neurons, which is responsible for the early symptoms of motor impairment of PD. These scans can reveal anomalies before motor signs apparent and worsen as neurodegeneration advances. However, especially in the initial phases of the disease, they have little to no association with the Unified Parkinson Disease Rating Scale [86].

In the brain, the protein known as the dopamine transporter (DAT) is essential for controlling synaptic dopamine levels. It regulates the amount of dopamine available for neurotransmission by recapturing it from the synaptic cleft and returning it to the presynaptic neuron. The density of DAT reflects the functioning of presynaptic dopaminergic neurons, making it an important biomarker for diseases especially PD, where dopaminergic neuron degeneration occurs [87]. In the context of PD, DAT testing is crucial for diagnosing the condition and the assessment of possible disease-modifying therapies, DAT testing is crucial. As dopaminergic neurons degenerate, the availability of DAT decreases, which can lead to higher measurement variability in patients compared to healthy controls.

DAT SPECT is a **FDA-approved** tool [88]. Most research on DAT-SPECT imaging of PD patients has demonstrated a high

diagnostic performance accuracy, with a specificity of 80% to 100% and a sensitivity of 79% to 100% [89].

The combination of hyposmia and DAT deficiency identified by DAT-SPECT can detect the risk of PD start, according to a clinical follow up study of 4 year by Jennings *et al.* (2017). A 5% annual decrease in DAT binding has a similarity to the initial phases of PD [90].

With improved spatial resolution and contrast, high-field MRI has been shown to more accurately distinguish between PD patients and healthy people. This makes it feasible to visualize the basal ganglia's boundaries and forms more clearly [91, 92]. Additionally, as compared to normal controls, MRI has shown that the substantia nigra's functional anisotropy and magnetization transfer ratio are reduced [93].

Chau *et al.* (2020) did a meta-analysis by screening the databases MEDLINE, Embase, and Scopus for studies published between 2012 and September 2019. The analysis includes 1508 participants from 19 studies, including 605 healthy controls and 903 idiopathic PD patients. Ultimately, the data indicated a specificity of 0.90 and a sensitivity of 0.94. Positive and negative test findings have respective probability ratios of 9.72 and 0.08. A pooled area under the receiver operating characteristics curve (AUC) of 0.98 was used to diagnose idiopathic PD. The visual evaluation of nigrosome-1 appearance at either 3 or 7 Tesla demonstrated remarkable diagnostic accuracy when used to differentiate between healthy individuals and idiopathic PD [94].

PET is a flexible and potent imaging method that makes it possible to examine in vivo neurological processes. By offering quantitative information along with functional insights on metabolism, cerebral blood flow, and receptor binding, it has made a substantial contribution to neuroscience research. Due to its costly price and necessity for extensive auxiliary equipment, especially on-site cyclotron, radiochemical laboratory and PET scanner, its application in clinical neurology is more limited than in oncology. PET offers an extremely accurate and sensitive in vivo measurement of local radiotracer activity [95].

Kerstens *et al.* (2020) conducted a study, which involved nine PD patients (Hoehn and Yahr stage < 3) who underwent two PET scans with [18F]FE-PE2I within a 7-28 day interval. The results of the study indicated that [18F]FE-PE2I PET measurements exhibited good repeatability and reliability, with absolute variability ranging from 5.3% to 11% across different brain regions. With ICCs ranging from 0.74 to 0.97, which were noticeably high, the measurements appear to be dependable and consistent. The less affected substantia nigra showed greater consistency compared to the more affected side, which may be attributed to lower DAT density in that region. The study concluded that [18F]FE-PE2I is a reliable biomarker for longitudinal studies of DAT decline in PD patients, with the ability to detect changes in DAT levels effectively. The results support the use of this radioligand in clinical settings for monitoring **disease progression** and evaluating treatment efficacy [96].

30 individuals with clinically confirmed PD or APS who received both conventional MRI and DTI were included in a retrospective analysis by Ananthasayanam *et al.* (2024). Retrospective data collection was used. The study's findings showed Of the 30 individuals, 46.7% had atypical parkinsonian syndromes (APS) and 53.3% had PD. In 83.3% of cases, DTI revealed abnormalities, although conventional MRI results were normal in 46.7% of cases. When it came to distinguishing PD from APS, diffusion tensor imaging (DTI) outperformed traditional MRI with a specificity of 93.8% and sensitivity of 95.8%. The study concluded that DTI is an excellent imaging technique for the early detection and differentiation of parkinsonian diseases [97].

2. CONCLUSION

In conclusion, recent years have seen tremendous advancements in the search for PD biomarkers, which present encouraging opportunities for early diagnosis, monitoring the progression of the disease, and detection. The review highlights the importance of various biomarker categories, including cerebrospinal fluid (CSF) markers, blood based biomarkers, genetic markers, and imaging techniques, each contributing unique insights into the pathophysiology of PD.

Cerebrospinal fluid biomarkers, such as alpha-synuclein, amyloid beta, and tau proteins, have shown potential in differentiating PD from other neurodegenerative disorders, while blood based biomarkers like neurofilament light chain and alpha-synuclein present opportunities for non-invasive assessments. Genetic markers, particularly mutations in the SNCA and LRRK2 genes, provide valuable information regarding individual risk and disease progression. Imaging modalities, including MRI and PET, enhance diagnostic accuracy and facilitate the monitoring of neurodegenerative changes.

In spite of these advancements, challenges remain in standardizing biomarker assays and establishing their clinical use. The variability in biomarker levels among individuals and the overlap with other conditions necessitate further research to refine these tools for practical application in medical practices. In the end, incorporating biomarkers into standard clinical practice has the ability to entirely revolutionize PD management by facilitating personalized treatment strategies and enhancing patient outcomes. Continued efforts in this field are essential to fully realize the promise of biomarkers in enhancing the understanding and management of PD.

3. FUTURE IMPLICATIONS

Future research on biomarkers for PD should focus on standardizing assays, identifying novel biomarkers, integrating multi-omics approaches, conducting longitudinal studies, personalizing medicine, improving diagnostic accuracy, fostering collaboration and data sharing, validating biomarkers in clinical settings, addressing cognitive impairment, and considering ethical implications. These efforts will enhance diagnostic accuracy, monitor disease progression, and develop targeted therapies, ultimately improving patient outcomes.

Additionally, insights from cancer early diagnosis with the help of biomarkers can provide valuable lessons for PD research, emphasizing the importance of early detection and personalized treatment strategies. Cancer research has shown that biomarkers, including proteins, nucleic acids, and organic small molecules, are crucial for early detection and improved patient outcomes.

Similarly, in PD, the identification of accurate biomarkers is essential for distinguishing PD from other conditions and for early diagnosis, which can significantly improve therapeutic interventions. By adopting the multi-omics approaches and longitudinal studies used in cancer research, PD studies can enhance the early detection and monitoring of disease progression, leading to more effective and personalized treatment strategies.

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