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Blood-Based Biomarkers for Parkinson's Disease

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Abstract

There is a pressing need for biomarkers to diagnose Parkinson's disease (PD), assess disease severity, and prognosticate course. Various types of biologic specimens are potential candidates for identifying biomarkers – defined here as surrogate indicators of physiological or pathophysiological states – but blood has the advantage of being minimally invasive to obtain. There are, however, several challenges to identifying biomarkers in blood. Several candidate biomarkers identified in other diseases or in other types of biological fluids are being pursued as blood-based biomarkers in PD. In addition, unbiased discovery is underway using techniques including metabolomics, proteomics, and gene expression profiling. In this review, we summarize these techniques and discuss the challenges and successes of blood-based biomarker discovery in PD. Blood-based biomarkers that are discussed include α-synuclein, DJ-1, uric acid, epidermal growth factor, apolipoprotein-A1, and peripheral inflammatory markers.

Introduction

Parkinson's disease (PD), which manifests with a combination of motor and non-motor features, is the 2nd most common neurodegenerative disorder. The clinical diagnosis of PD (based on physical examination findings), when applied by movement disorders specialists, is of moderate to high accuracy (sensitivity of 88.2% and specificity of 95.4%) with positive predictive value of 85.7%) [1]. However, it is becoming increasingly clear, largely in the face of the multitude of agents that have failed to modify the course of the disease, that the detection of PD prior to the emergence of motor manifestations is likely key to impacting the underlying neurodegeneration and expression of the disease [Esupp1]. In addition, while standardized quantification of disease severity has been applied for decades to PD [Esupp2-4], these rely largely on clinical history and physical examination, in which a subjective component cannot be eliminated. Predicting which patients with PD will have a relatively benign versus a more severe disease course, such as the development of dementia, is also very difficult based solely on clinical grounds. Thus, the development of biomarkers to predict, diagnose, evaluate, and prognosticate PD and trajectories within PD is essential for both patient care and research.

In this review, we discuss general concepts and approaches to blood-based biomarker development. We describe some challenges encountered in the early stages of development

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of two candidate biomarkers, α-Synuclein and DJ-1, as well as the data supporting serum and plasma uric acid as a PD risk biomarker. We then elaborate on the blood-based biomarkers for PD that have been identified to date via an unbiased approach and have at least been preliminarily replicated (table 1).

General Concepts in Biomarker Development

A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [Esupp5]. Biomarkers can be conceptualized in terms of trait, state, and rate [Esupp6]. A trait biomarker indicates susceptibility to a disease, a state biomarker is diagnostic of a disease, and a rate biomarker tracks progression of the disease (and is thus important in, for example, assessing response to a therapeutic intervention). A biomarker can be clinical (for example, an objectively measured physical examination finding, such as performance on a cognitive test), imaging-based (such as volumetric quantification of a specific brain region on MRI), genetic (for example, MAPT H1/H1 genotype as an independent predictor of dementia risk in PD [esupp7]), or biochemical. Various biologic specimens are potential candidates for identifying biochemical biomarkers; these include cerebrospinal fluid, blood components, urine, and skin.

A blood-based biomarker is ideal given the accessibility and minimal invasiveness and cost of phlebotomy. However, several challenges to blood-based biomarker development exist. Obviously, a direct connection between the brain and peripheral blood is absent (particularly in the setting of an intact blood-brain barrier). Furthermore, blood, which can be conceptualized as consisting of plasma, serum, and cellular compartments, is a heterogeneous mixture of cells, proteins, lipids, and various metabolic products. However, despite these obstacles, several advancements in blood-based biomarker development in PD have occurred in recent years.

Two general approaches to biomarker development can be conceptualized. Candidate biomarker testing begins with a specific target (based on, for example, what is known about the pathophysiology of a disease or performance of a given biomarker in other fields) and assesses whether or not that target can serve as biomarker for a disease or other state in question. In contrast, in unbiased biomarker discovery, a wide array of potential biomarkers may be examined at once and then a few key candidates selected based on the strength of the signal detected and biologic plausibility. In either approach, once a potential biomarker is identified in a cohort of patients, replication of the performance of this biomarker in independent cohorts of patients, and using different methods of measuring the biomarker, is essential before the biomarker can be translated into widespread use in the research or clinical setting. Large scale collaborative studies utilizing stringent protocols for patient characteriziation and specimen collection are currently underway and will facilitate this (table 2).

Methods of Unbiased Biomarker Discovery

Methods of unbiased biomarker discovery include proteomics, metabolomics, and gene expression profiling.

Proteomics

Proteomics, broadly defined as the large-scale study of both the structure and function of many proteins, involves various methods including immunoassays, 2-dimensional gel electrophoresis (2-DGE) and liquid chromatography based high-resolution tandem mass spectrometry. Quality control measures are essential to ensure that false signals are not pursued (see discussion of Epidermal Growth Factor below for examples of quality control measures). There has been substantial preliminary progress in the application of proteomics to CSF for PD biomarker detection; application to blood is also underway [9], and successful examples are discussed further below and in table 1.

Metabolomics

Metabolomics (or metabolomic profiling) is the large-scale study of chemical metabolic processes, as reflected in the measurement of small-molecule metabolites. A biomarker resulting from metabolomic profiling could be a single molecule or a combination of several molecules that occur in a specific pattern in a given state reflecting various metabolic processes. One method of metabolomic profiling, liquid chromatography electrochemical array detection (LCECA) was applied to plasma samples from 66 PD patients and 25 controls [10]. Initial analysis of the metabolomic profiles clearly differentiated PD patients from controls, with separate analyses in only the unmedicated PD patients compared to controls confirming the initial results. Variables contributing most significantly to differentiation of the two groups were identified. These included uric acid and glutathione which were decreased and increased respectively in PD patients compared to controls, as has been reported in other studies [10]. These preliminary findings require confirmation but suggest that metabolomics holds promise for plasma-based biomarker development in PD.

Gene Expression Profiling

A microarray involves hybridization of a nucleic acid sample to a large set of oligonucleotide probes. Microarrays allow for testing of the parallel expression of thousands of genes in a given sample, and variations in genome-wide expression provide an avenue for biomarker discovery, as a means of identifying gene expression patterns specific to a disease state. To investigate whether a specific pattern of mRNA expression could distinguish between PD patients and controls, transcriptional profiling was conducted on RNA extracted from whole blood of 50 PD patients and 55 age-matched controls [11]. The discovery cohort involved samples from 31 PD patients, 17 healthy controls, and 18 disease controls with Alzheimer’s disease or progressive supranuclear palsy. The expression of a combination of 8 marker genes was found to significantly correlate with PD; an average expression value of the 8 marker genes within the PD and non-PD samples was calculated, as was a risk score. Authors in this study then tested this risk assessment model in an independent test set of samples from 19 PD patients, 5 healthy controls, and 15 disease controls with other movement or cognitive disorders. Individuals in the 2nd and 3rd tertile of risk (with higher tertiles indicating higher risk) had an odds ratio of 1.9 and 5.1,respectively, for actually having clinical PD, and this relationship remained after adjusting for age, sex, and dopamine replacement therapy [11].

The 8 gene markers that were identified are not known to be involved in a common biologic pathway or process, though all are expressed in the human brain. Two of the 8 genes, namely the vitamin D receptor gene (*VDR*) and the huntingtin interacting protein 2 (*HIP2*) have been related to PD pathophysiology, and a 3rd gene, *CLTB*, is involved in dopamine transporter endocytosis [11].

While these findings require further confirmation, they demonstrate the potential utility of gene expression profiling in identifying blood-based biomarkers for PD.

Candidate Blood-Based Biomarker Testing

α-Synuclein

The rationale for the examination of α-synuclein as a PD biomarker stems from the key role of this protein in PD pathogenesis, first uncovered by detection of mutations in the α-synuclein gene as a monogenic cause for PD [12], very shortly thereafter followed by reports that α-synuclein is the main protein contained in the defining neuropathological lesions (Lewy bodies) of PD [Esupp8]. Initially thought to be a strictly intracellular protein, its identification in both CSF and plasma provided evidence that it is secreted from cells [Esupp9]. Intensive efforts to study CSF α-synuclein as a diagnostic PD biomarker have been underway with some promise [13,14]. A blood based α-synuclein biomarker has not fared as well. Attempts to measure oligomeric species of α-synuclein [15], total α-synuclein [16], and phosphorylated α-synuclein [17] in plasma, all with the goal of developing blood-based biomarkers, have been reported. While a preliminary study comparing oligomeric α-synuclein levels in 34 PD patients and age-matched controls showed that a high signal (defined as >0.5 optical density) occurred in about 3.5 times more PD patients compared to controls [15], a study by the same group that then compared levels of various forms of α-synuclein (total, oligomeric, total phosphorylated, and oligomeric phosphorylated) in 32 PD patients and 30 controls was not able to reproduce these findings [17]. Various technical difficulties – including the high abundance of α-synuclein within red blood cells – as well as confounding variables, such as comorbidities existing in only one group, may account for the lack of reproducibility. Indeed, subsequent studies have reported both increases [esupp10] and decreases [esupp11] in plasma α-synuclein in PD patients compared to controls.

DJ-1

DJ-1 also emerged as a candidate biomarker in PD after mutations in the gene (originally called *PARK7*) encoding this protein were identified in familial PD [18]. Like CSF α-synuclein, CSF DJ-1 also shows promise as a PD diagnostic marker [19]. However, a study examining serum DJ-1 using enzyme linked immunosorbent assays (ELISA) in 95 PD patients and 70 healthy controls failed to find significant differences between the two groups [20].

To further clarify the utility of plasma DJ-1 and α-synuclein as PD biomarkers, Shi et al studied samples from 126 PD patients and 122 normal controls using a modified multiplex immunoassay that, compared to ELISA and Western blotting, reportedly demonstrated higher sensitivity, throughput, and efficiency [21]. Importantly, the effect of various factors

including hemolysis (measured via hemoglobin), platelet contamination [as reflected by soluble P-selectin levels), and age-dependence were also evaluated in this study. A positive correlation between hemoglobin and DJ-1 as well as P-selectin and DJ-1 was observed. Maximal cut-off values for hemoglobin and P-selectin were identified [below which minimal effect on plasma DJ-1 and α-synuclein levels by hemoglobin and platelets would occur). The contributions of different blood components to plasma levels of DJ-1 and α-synuclein were also assessed; more than 95% of plasma DJ-1 and α-synuclein were found to come from red blood cells [RBCs). Regarding the effect of age, a decrease in plasma DJ-1 and α-synuclein was detected in PD patients; only α-synuclein decreased with age in controls [21]. These aspects of the Shi et al study highlight important quality-control steps in biomarker development. Unfortunately, even after controlling for these potential sources of noise, PD and normal controls did not differ significantly in plasma levels of DJ-1 or α-synuclein, suggesting that they are not of utility as biomarkers for PD diagnosis and/or prognostication [21].

Further work from the same group has also evaluated total DJ-1 and DJ-1 isoforms in whole blood using two-dimensional gel electrophoresis and immunoblotting techniques, as well as mass spectroscopy for analysis of DJ-1 isoforms and post-translational modifications [2]. This study confirmed that total DJ-1 levels were no different between PD patients and controls. Among the post-translational modifications identified, however, a specific and sensitive assay could be developed for the 4-hydroxy-2-nonenal [4-HNE) modification, often indicative of oxidative stress. Fractions of specific isoforms of HNE-modified DJ-1 were found to be significantly different in PD patients compared to controls and in late-stage PD compared to early-stage PD [2]. These findings were replicated in a cohort of 84 PD patients [24 early, 30 intermediate, and 30 late-stage) and 30 controls [2].

Uric Acid

Relevance of uric acid in PD pathophysiology was first suggested by the putative anti-oxidant properties of uric acid, the low levels of uric acid identified in the substantia nigra of PD patients [Esupp12], and the ability of uric acid to decrease dopamine oxidation [Esupp7], in the context of increasing evidence that oxidative stress contributes to the loss of dopaminergic neurons in PD. Its potential as a biomarker was first introduced by analyses of uric acid levels and risk of incident PD among 7,968 men enrolled in the Honolulu Heart Program [22]. In that cohort, serum uric acid levels were obtained at baseline and over a 30 year follow-up, during which 92 men developed idiopathic PD. Men with uric acid concentrations above the median at baseline had a 40% reduction in PD incidence compared to those below it [rate ratio 0.6) after adjusting for age or smoking history [22]. Two other prospective studies demonstrated similar findings. In the Rotterdam cohort [23], serum uric acid levels were obtained at baseline on 7,983 individuals over the age of 55, and 68 new cases of PD were detected over a mean of 9.4 years of follow-up. After adjusting for age and sex, higher uric acid levels were associated with lower risk of PD [hazard ratio per standard deviation of increase was 0.71), with evidence for a dose-dependent effect [hazard ratio for highest compared with lowest quartile was 0.42) [23]. In the Health Professionals Follow-up Study cohort [24], 18,018 men were followed for at least 15 years, and 84 cases of incident PD were identified. Compared to matched controls, in analyses adjusting for age, pack years

of smoking, and caffeine intake, the rate ratio for the highest quartile of serum uric acid levels compared to the lowest was 0.43. The rate ratio per unit [mg/dL) increase in urate concentrate was 0.76. The authors also conducted a meta-analysis of the results of their study along with those of the Honolulu Heart Program [22] and Rotterdam [23] cohorts and the pooled rate ratio of PD associated with 1 standard deviation increase in urate [1.32 mg/dL) was 0.80 [24].

The utility of uric acid as a marker of disease severity and/or progression [3] was investigated by utilizing data from the Parkinson Research Examination of CEP-1347 Trial [PRECEPT) cohort. This trial enrolled 806 de novo PD patients, 399 of whom had serum uric acid levels measured at baseline and underwent serial motor examinations as well as iodine 1 123-labeled β-CIT SPECT scans at baseline and approximately 2 years later. Sixty one percent of participants reached the end point of requiring dopaminergic therapy. The hazard ratio [HR) of reaching this end point declined with increasing concentrations of serum urate: subjects in the top quintile reached the end point at half the rate of the bottom quintile [HR 0.51); this association was stronger in men. Furthermore, a significantly lower rate of change in UPDRS score was found in those with the highest versus lowest sex-specific quintile of serum urate level; no such association was found in women. Finally, the percent of change in striatal iodine 1 123-labeled β-CIT uptake also declined with increasing urate concentrations.

Unbiased Blood-Based Biomarkers in PD

Epidermal Growth Factor

With the goal of identifying a blood-based biomarker for cognitive impairment [CI) in PD, we adopted an unbiased approach, utilizing a large-scale multiplex immunoassay platform [5]. Plasma samples from 70 PD patients were analyzed for 102 proteins simultaneously, and linear regression models were used to examine the association between each protein with cognitive performance on the Mattis Dementia Rating Scale [DRS), adjusting for age and gender. Eleven proteins showed nominally significant associations with cognitive performance, and epidermal growth factor [EGF) was identified as the top analyte. Furthermore, cross-sectional association between higher EGF levels and better cognition was replicated in an independent cohort of 113 PD patients, and low EGF values at baseline may also predict higher risk of development of dementia in the near term [hazard ratio >8 for development of dementia in follow-up for lowest quartile of EGF vs. all other quartiles) [5]. Our initial report that peripheral levels of EGF may be a promising biomarker for cognitive performance in PD has since been replicated by an independent group [25]. Specifically, Pellecchia et al [25] found in a cohort of 65 early, drug-naive PD patients, that lower serum EGF levels were correlated with poorer performance on tests of semantic fluency both at baseline and at two-years' follow-up.

ApoA1

In an approach similar to EGF, plasma samples from 152 PD patients were assessed by multiplex immunoassay for levels of 96 plasma proteins [4]. Of 11 proteins identified as being potentially correlated with age at PD onset, macrophage inflammatory protein-1β

[MIP-1 beta; lower levels associated with older age of onset) and apolipoprotein A1 [ApoA1; higher levels associated with older age of onset) showed the most significant associations. Based on biological plausibility and the availability of ApoA1-modifying medications, ApoA1 was further pursued as a potential biomarker of PD risk, and a 26% decreased risk of developing PD was noted for each increasing tertile of ApoA1 expression [hazard ratio = 0.742, 95% CI 0.606-0.909). These findings were then replicated in an independent cohort of 187 PD patients, in which a similar hazard ratio of 0.647 for each tertile increase in ApoA1 was found. In both the discovery and replication cohorts, ApoA1 values were also significant predictors of the UPDRS-III score [4].

To further confirm the association between ApoA1 and PD, plasma samples of 134 individuals from the from the Parkinson's At Risk Syndrome [PARS) cohort [26] were studied. ApoA1 levels were measured by a different method [ELISA) and correlated with putaminal dopamine transporter [DAT) uptake determined by [123I] ß-CIT SPECT [as a measure of dopamine transporter density, a proxy for striatal dopaminergic neuron terminal integrity). A significant association was found between DAT uptake and plasma ApoA1 levels, with lower ApoA1 levels associated with more severe DAT deficit [p=0.015), even after adjusting for age and gender. Intriguingly, PARS cohort subjects with low DAT uptake [DAT uptake≤80%) had the lowest ApoA1 levels [p=0.036 vs. normal controls), while PARS cohort subjects with normal DAT uptake [DAT uptake >80%) had levels close to those of normal subjects [4].

Since ApoA1 levels are modifiable with available drugs such as statin medications, identification of ApoA1 as a potential marker for PD risk illustrates the potential of unbiased biomarker discovery not only to identify biomarkers but also to elucidate possible pathophysiologic pathways and therapeutic targets for PD. Indeed, two recent studies have reported that the use of ApoA1- elevating statin medications is associated with decreased risk of developing PD in large population-based cohorts in the Unites States [27] and in Taiwan [28].

Other Potential Blood-Based PD Biomarkers

Because of evidence that neuroinflammation contributes to PD pathogenesis [29], inflammatory biomarkers have also been examined for their association with incident PD. As part of the Health Professionals Follow-up Study, 18,018 men provided blood samples [30], and within this cohort, there were 84 cases of incident PD. Plasma concentrations of interleukin-6 [IL-6) were positively associated with PD risk in multivariate analyses; those with IL-6 levels in the highest quintile had 3.5 times the odds of PD compared to those in the lowest quintile [30]. This finding awaits replication.

Also in line with the potential of inflammatory markers as blood-based biomarkers in PD, we have examined the peripheral expression of a large panel of proteins in 20 PD patients with GBA mutation [3 homozygote) compared to 87 PD patients without GBA mutation. Plasma levels of several monocyte-associated inflammatory mediators were identified and one, interleukin-8, was replicated in an independent cohort of 19 PD patients with GBA mutation vs. 41 PD patients without GBA mutations [6].

Conclusions

Blood-based biomarker discovery in PD is of high priority given the ease of sample collection. Biomarkers may be found by a candidate approach, or by unbiased methods for large-scale screening. To date, three blood-based biomarkers have been identified and replicated in independent cohorts of patients. Lower uric acid [22-24] levels may indicate increased risk for PD and severity of motor PD. Lower plasma ApoaA1 levels may also indicate increased risk for PD [4]. Finally, lower plasma EGF levels may be a marker for increased risk for cognitive impairment in PD [5]. As the important task of blood-based biomarker identification in PD continues, attention to meticulous methodology including assay validation and replication in independent cohorts will be key. To that end, the recent advent of large multi-site consortia for PD biomarker development such as the Michael J. Fox Foundation's Parkinson's Progression Marker Initiative and the National Institutes of Neurological Disease and Stroke Parkinson's Disease Biomarkers Program [table 2) hold great promise for moving this nascent area of translational research forward.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. Brain. 2002 Apr.125:861–70. [PubMed: 11912118]
2. Lin X, Cook TJ, Zabetian CP, Leverenz JB, Peskind ER, Hu SC, et al. DJ-1 isoforms in whole blood as potential biomarkers of Parkinson disease. Sci Rep. 2012; 2:954. [PubMed: 23233873]
3. Schwarzschild MA, Schwid SR, Marek K, Watts A, Lang AE, Oakes D, et al. Serum urate as a predictor of clinical and radiographic progression in Parkinson disease. Arch Neurol. 2008; 65:716–23. [PubMed: 18413464]
4. Qiang JK, Wong YC, Siderowf A, Hurtig HI, Xie SX, Lee VM, et al. Plasma apolipoprotein A1 as a biomarker for parkinson's disease. Ann Neurol. 2013 Feb 27.
5. Chen-Plotkin AS, Hu WT, Siderowf A, Weintraub D, Goldmann Gross R, Hurtig HI, et al. Plasma epidermal growth factor levels predict cognitive decline in Parkinson disease. Ann Neurol. 2011; 69:655–63. [PubMed: 21520231]
6. Chahine LM, Qiang J, Ashbridge E, Minger J, Yearout D, Horn S, et al. Clinical and Biochemical Differences in Patients Having Parkinson Disease With vs Without GBA Mutations. JAMA Neurol. 2013; 70:852–8. [PubMed: 23699752]
7. National Institute for Neurological Disorders and Stroke [NINDS). [09/2013] Parkinson's Disease Biomarkers Program [PDBP). Available at: pdbp.ninds.nih.gov/
8. Parkinson Progression Marker Initiative. The Parkinson Progression Marker Initiative [PPMI). Prog Neurobiol. 2011 Dec.95:629–35. [PubMed: 21930184]

9. Shi M, Caudle WM, Zhang J. Biomarker discovery in neurodegenerative diseases: a proteomic approach. Neurobiol Dis. 2009; 35:157–64. [PubMed: 18938247]
10. Bogdanov M, Matson WR, Wang L, Matson T, Saunders-Pullman R, Bressman SS, et al. Metabolomic profiling to develop blood biomarkers for Parkinson's disease. Brain. 2008; 1:389–96. [PubMed: 18222993]
11. Scherzer CR, Eklund AC, Morse LJ, Liao Z, Locascio JJ, Fefer D, et al. Molecular markers of early Parkinson's disease based on gene expression in blood. Proc Natl Acad Sci U S A. 2007; 104:955–60. [PubMed: 17215369]
12. Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science. 1997; 276:2045–7. [PubMed: 9197268]
13. Mollenhauer B, Trautmann E, Taylor P, Manninger P, Sixel-Doring F, Ebentheuer J, et al. Total CSF alpha-synuclein is lower in de novo Parkinson patients than in healthy subjects. Neurosci Lett. 2013; 532:44–8. [PubMed: 23149132]
14. Kang JH, Irwin DJ, Chen-Plotkin AS, Siderowf A, Caspell C, Coffey CS, et al. Association of Cerebrospinal Fluid beta-Amyloid 1-42, T-tau, P-tau181, and alpha-Synuclein Levels With Clinical Features of Drug-Naive Patients With Early Parkinson Disease. JAMA Neurol. 2013 Aug 26.
15. El-Agnaf OM, Salem SA, Paleologou KE, Curran MD, Gibson MJ, Court JA, et al. Detection of oligomeric forms of alpha-synuclein protein in human plasma as a potential biomarker for Parkinson's disease. FASEB J. 2006; 20:419–25. [PubMed: 16507759]
16. Tinsley RB, Kotschet K, Modesto D, Ng H, Wang Y, Nagley P, et al. Sensitive and specific detection of alpha-synuclein in human plasma. J Neurosci Res. 2010; 88:2693–2700. [PubMed: 20648655]
17. Foulds PG, Mitchell JD, Parker A, Turner R, Green G, Diggle P, et al. Phosphorylated alpha-synuclein can be detected in blood plasma and is potentially a useful biomarker for Parkinson's disease. FASEB J. 2011; 25:4127–37. [PubMed: 21865317]
18. Bonifati V, Rizzu P, van Baren MJ, Schaap O, Breedveld GJ, Krieger E, et al. Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. Science. 2003; 299:256–9. [PubMed: 12446870]
19. Hong Z, Shi M, Chung KA, Quinn JF, Peskind ER, Galasko D, et al. DJ-1 and alpha-synuclein in human cerebrospinal fluid as biomarkers of Parkinson's disease. Brain. 2010; 133:713–26. [PubMed: 20157014]
20. Maita C, Tsuji S, Yabe I, Hamada S, Ogata A, Maita H, et al. Secretion of DJ-1 into the serum of patients with Parkinson's disease. Neurosci Lett. 2008; 431:86–9. [PubMed: 18162323]
21. Shi M, Zabetian CP, Hancock AM, Ginghina C, Hong Z, Yearout D, et al. Significance and confounders of peripheral DJ-1 and alpha-synuclein in Parkinson's disease. Neurosci Lett. 2010; 480:78–82. [PubMed: 20540987]
22. Davis JW, Grandinetti A, Waslien CI, Ross GW, White LR, Morens DM. Observations on serum uric acid levels and the risk of idiopathic Parkinson's disease. Am J Epidemiol. 1996; 144:480–4. [PubMed: 8781463]
23. de Lau LM, Koudstaal PJ, Hofman A, Breteler MM. Serum uric acid levels and the risk of Parkinson's disease. Ann Neurol. 2005; 58:797–800. [PubMed: 16240356]
24. Weisskopf MG, O'Reilly E, Chen H, Schwarzschild MA, Ascherio A. Plasma urate and risk of Parkinson's disease. Am J Epidemiol. 2007; 166:561–7. [PubMed: 17584757]
25. Pellecchia MT, Santangelo G, Picillo M, Pivonello R, Longo K, Pivonello C, et al. Serum epidermal growth factor predicts cognitive functions in early, drug-naive Parkinson's disease patients. J Neurol. 2013; 260:438–44. [PubMed: 22911513]
26. Siderowf A, Jennings D, Eberly S, Oakes D, Hawkins KA, Ascherio A, et al. Impaired olfaction and other prodromal features in the Parkinson At-Risk Syndrome Study. Mov Disord. 2012; 27:406–12. [PubMed: 22237833]
27. Gao X, Simon KC, Schwarzschild MA, Ascherio A. Prospective study of statin use and risk of Parkinson disease. Arch Neurol. 2012; 69:380–4. [PubMed: 22410446]

28. Lee YC, Lin CH, Wu RM, Lin MS, Lin JW, Chang CH, et al. Discontinuation of statin therapy associates with Parkinson disease: A population-based study. Neurology. 2013; 81:410–16. [PubMed: 23884037]

29. McGeer PL, McGeer EG. Inflammation and neurodegeneration in Parkinson's disease. Parkinsonism Relat Disord. 2004; (Suppl 1):S3–7. [PubMed: 15109580]

30. Chen H, O'Reilly EJ, Schwarzschild MA, Ascherio A. Peripheral inflammatory biomarkers and risk of Parkinson's disease. Am J Epidemiol. 2008; 167:90–5. [PubMed: 17890755]

Table 1

Promising Blood-Based PD Biomarkers (only those in which replication in at least one independent cohort was achieved are included)

State Biomarkers	
Diagnostic markers	DJ-1 isoforms (6) Uric Acid (7)
Trait Biomarkers	
Motor disease severity	DJ-1 isoforms (6) ApoA1 (8) Uric acid (7)
Dementia	EGF (9)
Age-at-onset	ApoA1 (8)
GBA mutation carriers	Interleukin-8 (10)

Table 2

Parkinson's Disease Biomarker Initiatives

Initiative	Primary Sponsors	Goals
Parkinson's Disease Biomarkers Program (PDBP) (14)	National Institute of Neurological Disorders and Stroke (NINDS)	**i.** Bridge the gap between small pilot biomarker studies and validation studies of well replicated biomarker candidates **ii.** Support new and existing cohort studies that collect, into unified databases, standardized longitudinal clinical data and biospecimens across all stages of PD **iii.** Support development of analytical tools that will promote innovation around biomarker discovery
Parkinson's Progression Markers Initiative (15)	Michael J. Fox Foundation	**i.** Establish standardized protocols for acquisition, transfer and analysis of clinical, imaging and biospecimen data that can be used by the PD research community. **ii.** Investigate existing and identify novel clinical, imaging and biospecimen PD progression markers that individually or in combination will rapidly demonstrate interval change in PD patients in comparison to healthy controls or in sub-sets of PD patients defined by baseline assessments, progression milestones and/or rate of clinical, imaging or biospecimen change. **iii.** Optimize bioassays and conduct preliminary verification studies on promising biological markers using stored biospecimen