Parkinson’s disease – the continuing search for biomarkers

David P. Breen1,2,a, Andrew W. Michell2,a and Roger A. Barker1,2

1 Cambridge Centre for Brain Repair, University of Cambridge, Cambridge, UK
2 Department of Clinical Neurosciences, Addenbrooke’s Hospital, Cambridge, UK

Abstract

There is currently no well-established biomarker for Parkinson’s disease. The need to better diagnose the condition, define the subtypes of disease, and follow its course independent of any symptomatic drug effects is well-established. In this review, we will begin by reviewing the evidence for biological fluid biomarkers in Parkinson’s disease. We will then touch upon the role of brain imaging in diagnosis and defining prognosis, as well as the value of studying motor phenotype and its potential applications for characterising Parkinson’s disease subtypes with differing natural histories.

Keywords: biomarkers; motor phenotype; neurology; Parkinson’s disease.

Introduction

Parkinson’s disease (PD) is the second most common neurodegenerative condition in the UK, affecting 2% of adults over the age of 65 years (1). The pathological hallmark of the disease is progressive loss of dopaminergic neurones in the substantia nigra pars compacta. This is accompanied by microglial activation and intraneural accumulation of Lewy bodies (containing the protein α-synuclein) as the disease spreads from the brainstem to involve a range of other structures, including the cortex. In doing so, the condition evolves to encompass a broad range of motor and non-motor features (Figure 1). The extent to which this pathological cascade differs in terms of speed of progression and pathological extent may help to explain the different types of PD that are known to exist (2–4).

What will biomarkers be used for in PD?

Vast sums of money have been spent on the development of potential biomarkers in PD, with the hope and expectation that they will be able to help diagnose PD, track its clinical course, and predict disease complications. Biomarkers are also expected to inform us about the pathological basis of the condition, and thus allow for the design of new treatment strategies. To date, no treatment for PD has been proven to be neuroprotective in human trials (5), although recently completed trials of rasagiline show some promise (6).

It is unlikely that one single biomarker will be capable of performing all of these functions. In other words, different biomarkers will be required at different stages of the disease, depending on what questions are being asked.

Improving diagnostic accuracy

Several conditions mimic Parkinson’s disease in its early stages such as essential tremor, dystonic tremor, drug-induced parkinsonism and vascular parkinsonism. Similarly, it can be difficult to differentiate PD from the atypical parkinsonian syndromes which carry a worse prognosis [multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD)]. For this reason, not all cases of early PD are diagnosed correctly. Even when undertaken by a specialist, the sensitivity of a final ante-mortem diagnosis of PD was only 91% when compared to autopsy findings in one clinicopathological study (7).

Unfortunately, there is no reliable diagnostic test for PD at present. The diagnosis is based primarily on the UK Parkinson’s Disease Society Brain Bank clinical diagnostic criteria which incorporates bradykinesia, in combination with rest tremor, rigidity and/or postural instability (8). It is typically these movement problems which lead to patients consulting their general practitioner in the first place, by which time they have lost up to 70% of dopaminergic neurones in some parts of the substantia nigra (9). However, there is now a general consensus that the pathological process underpinning PD begins at least 5 years prior to the onset of motor symptoms (9, 10). During this time, the patient may exhibit non-motor features due to neuronal loss and neurochemical depletion outside the substantia nigra (including problems with smell, sleep, autonomic function, vision, cognition and mood). Diagnosing PD patients earlier using biomarkers is an exciting prospect, especially as we move towards an era of novel neuroprotective therapies. However, this relies on...
knowing that all patients with ‘pre-PD’ will convert to ‘overt motor PD’ – studies to clarify whether this is the case are currently ongoing.

Monitoring disease progression and predicting disease complications

The rate of progression of PD symptoms and signs varies significantly between patients, and the factors governing this disease heterogeneity are poorly understood. In addition to advancing motor disability, patients with PD accumulate a variety of non-motor problems during the course of their disease, including cognitive impairment and dementia. Biomarkers are urgently needed to identify patients at increased risk of disease complications so that they can be counseled and managed appropriately. Such biomarkers may also help to assess new disease-modifying agents, as well as provide the basis for stratification of disease by subtype.

Why do we need a range of different biomarkers?

The problem with wet biomarkers [cerebrospinal fluid (CSF), blood, urine] and imaging techniques in PD is that we do not fully understand the pathologic substrates of PD and their relationship with clinical phenotype. For example, symptoms and signs can fluctuate dramatically over minutes and hours, whereas the underlying pathology does not. Thus, while markers of underlying pathology are undoubtedly essential, they are unlikely to be able to reflect the clinical phenotype accurately or the progression of disability.

At the other end of the spectrum, markers of clinical phenotype include measures of motor performance, movement and disability. Given the heterogeneity of PD (11) and the clinico-pathological dissociation often observed, it is inevitable that markers of motor impairment or disability do not necessarily correspond precisely to markers of cellular pathology. This has important implications for the assessment of a possible new biomarker. For example, there is no reason that a new objective marker of motor impairment should correspond to a positron emission tomography (PET)-scan assessing nigrostriatal dopaminergic function or even to existing motor assessments – in fact an improved biomarker would correspond precisely to neither.

The licensing of interferons as disease-modifying treatment in multiple sclerosis provides an interesting comparison with neuroprotection in PD. Pathological biomarkers alone are insufficient evidence for licensing authorities – protecting cells does not necessarily make people better (12). Licensing of interferons only occurred once an effect was shown both on function (in this case the expanded disability scale) and on imaging (which provided a pathological rationale for the observed effect). In PD, there is not yet an accepted surrogate marker of nigrostriatal function, but markers of function are available and could be improved.

In this review, we will begin by reviewing the evidence for biological fluid biomarkers, concentrating on those in the CSF which have shown the greatest promise. We will then touch upon the role of brain imaging in diagnosis and prognostication, as well as the value of studying patients’ motor phenotype and potential applications for this in the future. The genetic aspects of PD are covered elsewhere in this issue.

Biological fluid biomarkers

To date, the search for biomarkers has concentrated on single proteins implicated in the hypothesised model of PD pathogenesis. There is now considerable evidence pointing towards mitochondrial dysfunction (13–15), increased oxidative stress (16), inflammation and microglial activation (17, 18), and impaired protein degradation (19) as being at the heart of PD pathogenesis. These, in turn, are believed to cause the pathological protein aggregation (particularly involving α-synuclein) and cell death seen in PD (20). Precisely what
triggers this process and why dopaminergic neurons in the substantia nigra are preferentially affected is unclear. Candidate biomarkers have been studied in a variety of biological fluids and we will look at the most promising of these in turn.

**CSF biomarkers**

**Markers of mitochondrial dysfunction and oxidative stress** Oxidative stress can be quantified indirectly in the CSF by studying oxidatively modified proteins or alterations in antioxidant concentrations. Hong et al. used a robust Lumex assay to show that there was significantly reduced concentrations of DJ-1, a mitochondria-related antioxidant, in the CSF of 117 PD patients compared to both 50 Alzheimer’s disease (AD) patients and 132 controls (21). Lower concentrations of other antioxidants, such as Cu/Zn-dependant superoxide dismutase and ceruloplasmin, have also been found in the CSF of PD patients compared to controls (22). Changes in the concentrations of oxidative stress-related proteins have also been detected. In a small study, the concentration of nitrated manganese superoxide dismutase was increased in a group of 10 PD patients compared to controls (23).

**Markers of protein aggregation** In PD, monomeric α-synuclein aggregates into soluble oligomers and then insoluble fibrils, thereby becoming “toxic” to the cell (24). Laboratory ELISA methods have tended to measure only total α-synuclein from biological fluids, and studies have yielded conflicting results. Three studies have found decreased total α-synuclein in the CSF of PD patients compared to controls (21, 25, 26). In the largest of these, Hong et al. found reduced total α-synuclein in the CSF of PD patients compared to AD patients (sensitivity 93%, specificity 39%) and controls (sensitivity 93%, specificity 63%) after controlling for blood contamination (21). The reason for this is thought to be sequestration of α-synuclein within nerve cells in the brain of PD patients. There was no association between α-synuclein concentrations and disease severity, in contrast to a previous study (25). Two studies found no difference in concentrations of total α-synuclein between PD patients and controls (27, 28).

A specific ELISA for oligomeric α-synuclein has now been developed. One study used this approach to show that oligomeric α-synuclein was increased in the CSF of patients with Lewy body disease (PD and Dementia with Lewy bodies) compared to non-Lewy body disease subjects (controls and tauopathies) (29).

Osteopontin, another protein expressed in Lewy bodies, has been shown to be increased in the CSF of PD patients compared to controls (30). Tissue transaminase, which promotes α-synuclein cross-linking, is reported to be increased almost 10-fold in PD patients compared to controls, although there is considerable overlap between controls and certain PD patients limiting its diagnostic utility (31). Neurofilaments are part of the cellular cytoskeleton and have been shown to be increased in PSP and MSA compared to PD (32, 33). By reflecting the more rapid progression of cellular loss in these conditions, this biomarker may have a role in differentiating PD from atypical parkinsonian syndromes in the future.

**Markers of AD-type pathology in PD dementia** Even at the time of diagnosis, many PD patients have neuropsychological deficits, including frontal executive dysfunction, visuospatial impairment and memory impairment (2), and these constitute risk factors for progression to more severe cognitive impairment (including dementia) (3, 34). Up to 80% of PD patients will develop dementia during the course of their illness (35, 36). Research has implicated both PD-type pathology (LeWey body accumulation) and AD-type pathology (amyloid deposits and neurofibrillary tangles) in the aetiology of PD dementia. More specifically, it has been suggested that AD-type pathology may be associated with memory impairment, whereas Lewy body disease may be responsible for executive and visuospatial impairments.

This hypothesis is supported by a recent study, in which amyloid-β peptide CSF concentrations were significantly reduced in 109 PD patients – mostly drug naïve – compared to controls (37). Furthermore, there was a significant linear association between amyloid-β concentrations and memory performance, but not visuospatial or executive dysfunction. Compta et al. also studied 40 PD patients [20 PD dementia (PDD) and 20 PD with no dementia (PDND)] and 30 controls (38). Concentrations of total-tau (a marker of axonal death) and phosphorylated-tau (a marker of neurofibrillary tangles) were higher in the CSF of PDD patients than PDND patients and controls. Amyloid-β concentrations in the CSF ranged from high (controls) to intermediate (PDND) to low (PDD) concentrations, and may prove to be a useful marker of early cognitive dysfunction.

**Other markers** In a recent study, CSF concentrations of the endocannabinoid anandamide in untreated PD patients were twice as high as normal controls and those receiving dopamine replacement therapy (39). Since a balance between endocannabinoid and dopamine-dependant systems is believed to underlie physiological motor control, this may reflect a compensatory response to central dopamine depletion in these patients.

**Blood and urine biomarkers**

Measurement of biomarkers in blood and urine is appealing because they are much easier to obtain. α-synuclein can be detected in plasma, but is an unreliable marker of central nervous system pathology. While El-Agnaf et al. found significantly increased concentrations of oligomeric forms of α-synuclein in plasma samples of PD patients, there was significant overlap with controls (40). Even when haemolysis and platelet contamination were taken into account, concentrations were not significantly different in PD patients in another study (41). Our group also found a high-level of intersubject variability in concentrations of full length and truncated α-synuclein in platelets of PD patients, making this a poor diagnostic biomarker (42). One small study did report
that the SNCA gene, which is responsible for the production of α-synuclein, is upregulated in the skin fibroblasts of patients with PD, but not in controls or individuals with AD (43).

Increased serum concentrations of soluble tumour necrosis factor-α-receptor 1 have been found in PD patients compared to controls (44), further implicating the aetiological importance of inflammation in idiopathic PD. A recent study found that a variety of serum markers of oxidative damage were elevated in a group of 61 PD patients compared to controls (45), which is consistent with the finding that lower serum ceruloplasmin concentrations have been shown to correlate with younger age of PD onset (46). Others have used a 2D-gel generated serum protein biomarker panel to show that a panel of 21 proteins can distinguish PD patients from controls with a sensitivity and specificity of 93% (47). DJ-1 has also been found to be increased in the plasma of PD patients in parallel with disease severity (48), but this has not been replicated elsewhere (41).

Interestingly, the urine concentration of 8-hydroxydeoxyguanosine, another marker of oxidative stress, has been found to be increased in line with PD progression in one study, although concentrations are similar in MSA, diabetes and elderly controls (49). This protein was also found to be increased in the plasma of PD patients in another metabolomic study (50).

**Systems approach to identification of biomarkers**

The biomarkers described so far have been studied by researchers because of their suspected involvement in PD pathogenesis. However, it is also possible to use a systems approach to uncover novel PD biomarkers. High-throughput systems can now be used to analyse large numbers of low-molecular weight compounds within a particular tissue sample and to organise the data into a format suitable for data mining. This was done without a priori guessing on what is likely to be most informative.

For example, in a metabolomic profiling study of 66 PD patients and 25 controls, there were significantly altered concentrations of two antioxidants in the plasma of the PD group; a reduction in uric acid and an increase in glutathione concentrations (50). This is in agreement with previous studies showing that higher uric acid concentrations are associated with a lower risk of PD and a slower rate of disease progression (51). Elevated concentrations of oxidised glutathione have also been demonstrated in the plasma of PD patients (52). This approach may allow identification of new biomarkers and continue to shed light on the underlying pathogenesis of PD. However, such studies are not easy to interpret as there are multiple confounders relating to the effects of medication, diet and environmental factors. Studies of this type can therefore produce different results in the hands of different investigators (53). Proteomic approaches have also been employed in CSF studies, one of which identified eight potential biomarkers in PD including tau (54).

**Conclusions on “wet” biomarkers**

While the concentrations of several proteins are significantly altered in biological fluids of PD patients compared to controls, none of these biomarkers are sufficiently reliable to be clinically useful at present. One of the problems is the pathological overlap between PD and other neurodegenerative conditions such as MSA, as well as the heterogeneity of PD itself. Technical problems such as the influence of circadian rhythm and traumatic lumbar puncture on CSF protein concentrations also need to be considered. The toxic, oligomeric form of α-synuclein is the most promising target to help differentiate the synucleinopathies (including PD) from tauopathies and other individuals. CSF biomarkers of oxidative stress (DJ-1) and cell death (neurofilaments) may be useful in monitoring disease progression, whereas biomarkers of AD pathology (amyloid-β and tau) may be able to identify patients at increased risk of developing a dementia with their PD (Table 1).

**Brain imaging biomarkers**

Several imaging modalities can facilitate the early accurate diagnosis of PD. Single photon emission computed tomography (SPECT) uses the density of a dopamine transporter (DAT) radiolabelled ligand (usually 123I-FP-CIT) as a marker of dopamine terminal innervation. Uptake is normal in controls and patients with essential tremor and drug-induced parkinsonism, whereas there is reduced radiotracer uptake in the putamen and caudate of PD patients. Striatal DAT imaging with SPECT can differentiate between clinically probable PD and essential tremor with a sensitivity of 79%–100% and specificity of 80%–100% (55). However, DAT imaging cannot effectively differentiate between PD, MSA, PSP or CBD.

To achieve this, advanced magnetic resonance (MR) techniques may be helpful. Diffusion weighted imaging (56), diffusion tensor imaging (57), inversion recovery sequencing (58), volumetric imaging (59) and spectroscopic imaging (15) have all shown promise in being able to differentiate PD from atypical parkinsonian syndromes, but have not yet been widely accepted.

In the hands of some investigators, transcranial sonography also shows increased echogenicity of the substantia nigra in PD (probably due to increased iron concentration). In a study of 60 patients with early parkinsonism of unknown cause, baseline transcranial sonography had a sensitivity of 91% and specificity of 82% compared with an endpoint PD diagnosis at 1 year (60). However, this technique is very operator-dependant and is not commonly used in routine clinical practice.

PET has the potential to become an important tool in diagnosing PD, tracking disease course over time and predicting late complications. As well as helping to differentiate PD from atypical parkinsonian syndromes, resting state PET shows impaired glucose utilisation in PD patients with cognitive impairment, with the posterior parietal and temporal association areas being most affected (61). Various PET ligands have also been developed to study β-amyloid plaque...
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<th>Study</th>
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<td>Hong et al. 2010 (21)</td>
<td>117 PD, 50 AD, 132 controls</td>
<td>α-Synuclein and DJ-1</td>
<td>CSF</td>
<td>Significant reduction of α-synuclein and DJ-1 in PD patients compared with AD and controls after controlling for blood contamination and age</td>
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<td>Abdo et al. 2007 (32)</td>
<td>31 PD, 19 MSA</td>
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<td>Brettschneider et al. 2006 (33)</td>
<td>22 PD, 21 MSA, 21 PSP, 6 CBD, 45 controls</td>
<td>Neurofilament heavy chain</td>
<td>CSF</td>
<td>Concentrations significantly higher in MSA and PSP compared with PD</td>
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<tr>
<td>Alves et al. 2010 (37)</td>
<td>109 PD, 20 AD, 36 controls</td>
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<td>Prognostic</td>
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<td>Compta et al. 2009 (38)</td>
<td>40 PD (20 with PDD and 20 with PDND), 30 controls</td>
<td>Total-tau and phosphorylated-tau</td>
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<td>Concentrations significantly higher in patients with PDD compared to PDND and controls</td>
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<td>Shi et al. 2010 (41)</td>
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<td>Bogdanov et al. 2008 (50)</td>
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<tr>
<td>Zhang et al. 2008 (54)</td>
<td>40 PD, 48 AD, 105 controls</td>
<td>Proteomic profile</td>
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<td>95% agreement between biomarker panel and expert diagnosis of PD and controls, 75% agreement for AD</td>
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load (14C-PIB-PET) (62) and binding to peripheral benzodiazepine receptors on activated microglial cells as a marker of cerebral inflammation (14C-PK11195) (18). These imaging strategies may help to identify those patients at high risk of PD dementia. However, PET imaging is expensive and facilities are not widely available, therefore further longitudinal studies will be required before deciding whether it is cost-effective, or simply an interesting research tool to help elucidate the underlying pathophysiology of the condition.

Conclusions on imaging biomarkers
Unlike PET with specialist ligands, MR and DAT imaging facilities are widely available and in many ways are attractive as potential PD biomarkers. However, these imaging modalities struggle to produce consistent results due to problems with sensitivity and further work is required to prove their efficacy.

Motor biomarkers of PD

Why study motor markers of PD?

Drugs that may be disease-modifying are also likely to have symptomatic effects. So why bother measuring motor impairment, or the consequent disability, when the neuroprotective effect may be masked by symptomatic effects? One reason is that since there is no proven biomarker of PD, it is essential that we are able to demonstrate changes in clinical impairment and disability as best we can for drug licensing purposes.

At present, clinical trials of candidate neuroprotective agents follow designs incorporating a delayed start or drug withdrawal phase to try to overcome the symptomatic effect of the medication (63). Such trial designs have their problems (64, 65), for example interpretation of the DATATOP trial of selegiline was compromised by the 40 days half-life of brain monoamine oxidase-B inhibition (66). Having said that, symptomatic treatment with dopaminergic agents probably affects radioligand binding or metabolism, compromising the ability of PET to reflect nigrostriatal dopaminergic integrity and disease progression. Therefore, although measures of motor impairment are often overtly affected by symptomatic treatments, it is likely that other biomarkers of the underlying PD pathology are also affected in unanticipated ways.

It is a common misunderstanding that measurement of motor impairment only quantifies the clinical examination. For instance, the study of saccadic eye movements in PD may be interpreted in light of the Linear Approach to Threshold with Ergodic Rate (LATER) theory of decision-making (67).

It seems reasonable to hope that markers of motor impairment may correspond to eventual disability in PD. For example, in a population-based PD cohort followed longitudinally for 4–8 years, deterioration in physical mobility was the single most important factor contributing to decline in health related quality of life (68). Previous longitudinal studies have also stressed the significance of reduced mobility to health status in PD (69). Furthermore, a recent review of PD clinical trials found that bradykinesia, rigidity and activities of daily living deteriorated early in patients with PD, while gait impairment (plus sleep, cognition and speech disturbance) progressed linearly in proportion to disease duration (70).

Objective measures of motor impairment

Measurement and quantification of motor impairment in PD is typically performed using the Unified Parkinson's Disease Rating Scale (UPDRS). This involves a structured, subjective assessment by a clinician and is known to be susceptible to placebo effects and variation amongst raters (71). In this regard, a truly objective automated measure of motor impairment would be an improvement, provided it was relatively quick, easy to perform and non-invasive.

The likely magnitude of any neuroprotective effect in clinical trials is small. For example, the difference between the delayed-start and early-start groups in the ADAGIO and TEMPO trials of rasagiline was only about 2 UPDRS points (6, 72). Furthermore, the UPDRS rating scale is not linear; in other words, there are non-equivalent differences between subjectively scored points. Thus, a more sensitive measure of motor function is likely to prove advantageous in detecting small effects.

The ideal motor biomarker

The ideal marker of motor impairment would maximally capture the abnormal movement seen in PD, representing it accurately and reproducibly on a scale that increases linearly with disease progression. We know that PD is heterogeneous, affecting patients in different ways. Typically, the motor abnormality progresses by spreading from one side of the body to become more generalised, increasing in severity and changing in type (tremor is present early, dyskinesias and freezing are later manifestations). We do not know how best to measure, quantify or characterise the motor impairment of PD.

One appealing approach would be a non-hypothesis driven approach, in some ways analogous to systems biology ‘omics’ in which the aim is to measure everything and then fish out important trends to inform us about, for example, disease progression or theories of motor control. We have previously used the term ‘clinical phenomics’ to describe such an approach to the measurement of clinical phenotype – in this case motor impairment (73). The challenges to such an approach are not insignificant, both from a technical perspective in recording the measurements, but also from a statistical viewpoint in analysing megavariable longitudinal data.

It is not clear what task patients should perform when motor impairment is being recorded, and it may be that the best approach is to approach the disease in reverse. That is, to find out what sorts of motor disabilities patients experience and then work backwards to design a test of motor impairment around that task. For example, if the disability involves slowness of gait, the measurement of motor impair-
ment should be taken while walking, but if the disability involves illegible handwriting then that would need assessment. By objectively and accurately measuring motor impairment in this way, it is more likely to correspond to disability. In fact, it may be that by questioning patients about motor disability in detail, with a view to finding measurable correlates, that current functional rating scales are improved or redesigned. This of itself may be extremely helpful, as there is evidence that currently available scales, such as the activities of daily living subsection of the UPDRS, vary less with short-term fluctuations in motor ability, and may themselves be good measures of disease progression (74).

### Conclusions on motor biomarkers

We have entered an era of disease-modifying treatments for PD and there is an urgent need for surrogate biomarkers of clinical impairment and disability. Sensitive, objective assessment of motor phenotype – potentially using a non-hypothesis driven approach – would be a big step forward in helping to identify effective neuroprotective agents by acting as a surrogate marker of disease progression.

### Conclusions

At the present time, there is no well-established biomarker for PD. The need to better diagnose the condition, define the subtypes of disease, and follow its course independent of any symptomatic drug effects is desperately needed. A number of different approaches have been summarised in this review, and different biomarkers (or a combination of them) are likely to be needed in the future.

Our own work has shown that elderly PD patients with a Postural Instability and Gait Disorder motor presentation and poor performance on neuropsychological tasks with a posterior cortical basis (including semantic fluency and the ability to copy interlocking pentagons) are much more likely to dement early in the disease course, especially if they carry the H1 tau haplotype (3, 4). Enriching for this population in PD trials may be a better way of seeing whether a disease-modifying therapy really does reduce the rate of conversion to dementia over time. This type of research is expensive because it takes time, but we may have to be patient as the search for a quick, cheap, reliable biomarker for disease progression in PD continues.

The chance of finding robust biomarkers increases each year as we learn more about PD pathogenesis. Indeed, the realisation that PD is more than a motor disorder involving the nigrostriatal dopaminergic pathway has raised several new possible biomarker targets. Technological advances in systems analysis have also enabled researchers to start identifying biomarkers using high throughput techniques. However, the use of biomarkers as a useful adjunct in PD remains a long way off and thinking about how we can best deploy the biomarkers we already have remains a challenge in itself.

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### References


