Clinical prediction of Parkinson’s disease: planning for the age of neuroprotection

R B Postuma,1,2 J F Gagnon,2,3 J Montplaisir2,3

ABSTRACT
As a chronic progressive disease, Parkinson’s disease (PD) has a presymptomatic interval; that is, a period during which the pathological process has begun, but motor signs required for the clinical diagnosis are absent. The ability to identify this presymptomatic stage may be critical in the development and eventual use of neuroprotective therapy. Recently proposed staging systems of PD have suggested that degeneration may occur initially in areas outside the substantia nigra, suggesting that non-motor manifestations may be markers of presymptomatic PD. Decreased olfaction has recently been demonstrated to predict PD in prospective pathological studies, although the lead time may be relatively short, and the positive predictive value is low. Idiopathic RBD has a very high predictive value, with approximately 50% of affected individuals developing PD or dementia within 10 years. This implies that idiopathic RBD patients are ideal candidates to test potential preclinical markers. However, the specificity of symptom screens for RBD is not established, not all persons with PD develop RBD, and there are only limited ways to predict which RBD patients will develop PD. Other simple screens based upon autonomic symptoms, depression and personality changes, quantitative motor testing and other sleep disorders may also be useful markers, but have not been extensively tested. Other more expensive measures such as detailed autonomic testing, cardiac MIBG-spectroscopy, dopaminergic imaging and transcranial ultrasound may be especially useful in defining disease risk in those identified through primary screening.

INTRODUCTION
As a progressive neurodegenerative disorder, Parkinson’s disease (PD) does not start suddenly; therefore, there is a period during which degeneration is ongoing, but disease is not yet clinically evident. This implies potential to predict PD by detecting this presymptomatic threshold with clinical examination, symptom screens and other markers. This review summarises the goals of PD prediction, the pathophysiological basis for prediction and what is currently known about predictive markers of PD, and discusses how these markers could be implemented in the future, particularly in an age when neuroprotective therapy has been developed.

WHY IS PREDICTION IMPORTANT?
Development of predictive markers for PD will require a very substantial research investment, and clinical application of predictive methods in the future will be even more costly. Therefore, before beginning to study disease prediction, it is first essential to determine why it is important to do so. Understanding the purpose provides the framework with which potential predictive strategies can be evaluated and compared. One important question is whether foreknowledge of PD is, in itself, a sufficient motivation for using predictive measures. Theoretically, knowledge of an impending neurodegenerative condition could help in planning retirement, finances, family structure, etc. On the other hand, such knowledge could lead to distress, premature adoption of sick role, discrimination or even suicide. An analogous experience of prediction for knowledge’s sake is presymptomatic testing for Huntington’s disease (HD), for which despite having broad availability, only between 4% and 24% of eligible persons elect to have testing. One important difference, however, is that unlike HD, PD manifestations are treated very effectively with medications; surveillance for PD can result in early symptomatic improvement, perhaps with long-term benefits on quality of life.

The most important reason to develop predictive agents becomes apparent upon imagining the future of neurology. The most elusive goal in neurodegeneration is a neuroprotective agent, that is, a therapy to slow or stop the underlying degenerative process. If and when neuroprotective treatment becomes available, it will become essential to identify patients as early as possible. A partially effective agent with minor utility in established disease might slow or even prevent the onset of clinical disease if given in preclinical stages. Therefore, the major use of predictive markers of PD will be in the future, and present efforts to design predictive markers must plan for an age of neuroprotective therapy.

WHO COULD BE TESTED?
In an age of neuroprotection, those at high disease risk will be motivated to undergo even relatively invasive procedures to determine need for therapy. However, PD has an approximate prevalence of 1.5% at age 65, and it is unclear whether high-risk populations will be easily identifiable. Family members of patients with PD could be one potential high-risk population; however, RR for first-degree relatives is approximately 2–3, implying a increase in risk to only 4%. Defined causative gene mutations are identifiable in some patients, and these gene carriers are ideal candidates for studies of predictive markers. However, twin studies have found a low genetic contribution to PD risk in persons over 50 (at least in Caucasian populations), suggesting that the proportion of PD patients with identifiable causative mutations is

1Department of Neurology, McGill University, Montreal General Hospital, Montreal, Quebec, Canada
2Centre d’étude du sommeil, Hopital du Sacre-Coeur, Montreal, Quebec, Canada
3Département de psychiatrie, Université de Montréal, Canada

Correspondence to
Dr Ronald B Postuma,
Department of Neurology,
L7-312 Montreal General Hospital,
1650 Cedar Avenue,
Montreal, Quebec H3G 1A4;
Canada;
ronald.postuma@mcgill.ca

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unlikely to grow substantially. Many environmental risk factors (eg, pesticide use, non-smoking) increase the risk of PD. However, other than age, either ORs for risk factors are low (ie, ~2) or exposures are rare.

If there are no methods to reliably identify persons at substantial risk of disease, screening in an age of neuroprotection may need to be population-wide. This adds considerable additional challenges—in addition to being sensitive and specific, screens must now also be non-invasive and inexpensive. Invasive or expensive tests may eventually be used predominantly as secondary confirmation of a positive screen or primary screens for the few who are definable as high-risk.

**PATHOPHYSIOLOGICAL BASIS OF PREDICTOR DEVELOPMENT—PRECLINICAL PD**

The first major principle behind the development of predictive markers is redundancy/compensation. Pathological and neuroimaging studies suggest that motor signs of PD only develop once 50–70% of SNpc neurons have degenerated. Since neurodegenerative disorders are progressive, less complete stages of degeneration in the SNpc should be detectable. This is the basis for the use of dopaminergic imaging and quantitative motor testing as disease predictors. Similar redundancy may be present in other non-motor areas (see below), implying that sensitive markers of these systems could predict preclinical disease sooner than clinical symptoms or signs.

Perhaps the most important principle presently guiding predictor development is that PD may not start in the substantia nigra (SNpc). According to a proposed staging system by Braak et al, the first stage of PD involves deposition of α-synuclein in the anterior olfactory nucleus and dorsal motor nucleus of the vagus. Peripheral autonomic ganglia and unmyelinated lamina-1 spinal cord neurons may also be involved in stage 1.6 Stage 2 is characterised by medullary and pontine involvement affecting lower raphae, the reticular formation and the coeruleus/subcoeruleus complex. Stage 3 affects midbrain (including SNpc), and at Stages 4–6 cortical structures are affected. With some important modifications and exceptions, investigators in other groups have generally confirmed these findings.7 However, some important limitations should be noted. It is unlikely that the same pathological process is followed universally; subsequent studies have found variable progression patterns with onset of disease in the SNpc or multicentrically.7–10 This model assessed α-synuclein deposition, which may not correlate with neurodegeneration; in some cases, even advanced stages of α-synuclein deposition can be present without clinical parkinsonism or dementia.11 Clinical histories of patients were incomplete, limiting clinicopathological correlation. Brains were selected for detailed analysis if there was synuclein deposition in the dorsal motor vagus, introducing a potentially important selection bias. Finally, speed of progression through early stages is unknown—rapid progression implies a short premotor interval, limiting the effectiveness of predictive markers. Despite these limitations, the recognition that initial pathology of PD may occur outside the SNpc suggests that screening for non-motor manifestations may detect earlier stages of PD.

**POTENTIAL MARKERS**

For the purposes of this review, a clinical predictive marker for PD will be arbitrarily defined as a sign of insipient neurodegeneration present before PD can be diagnosed clinically. Factors that are generally considered risk factors but not preclinical signs of disease (eg, pesticide use, non-smoking) will not be discussed (note that it is impossible to be sure that some ‘risk factors’ are not preclinical signs). Ongoing research is identifying CSF and serum markers of disease.12 This complex area has, so far, not found reliable predictive biomarkers—for space reasons, this field will not be discussed further.

There are a considerable number of potential markers for prediction of PD. To aid in conceptualisation, the discussion of these markers will be divided according to Braak stages.

**‘STAGE 1’ MARKERS**

**Olfaction**

In Braak Stage 1 PD, synuclein deposition predominates in the anterior olfactory nucleus and, to a lesser extent, in the olfactory bulb.5–13 Accordingly, the large majority of PD patients have severe olfactory loss at disease onset.14 Olfaction is usually normal or only mildly impaired in other parkinsonian disorders.14 Olfactory loss may also be an important preclinical marker of dementia, especially Lewy body dementia (LBD)15 and Alzheimer’s disease (AD). In general, olfactory loss is less severe in AD than in LBD, and there have been suggestions that complete anosmia may help identify LBD in a patient with dementia.15 A major advantage of olfactory tests is that they are inexpensive and non-invasive. The commonest tests include the University of Pennsylvania Smell Identification Test,16 a forced-choice scratch-and-sniff test and ‘Sniffin’ Sticks’, which are felt pens impregnated with odours.17 The latter method tests olfactory threshold as well as discrimination, although the former can be self-administered (even by post) and is more widely used.

There is good evidence that olfactory loss can predict PD. One study measuring olfaction in 400 first-degree relatives of PD patients found that those with impaired olfaction had dopaminergic denervation on 6-CIT SPECT.18 Two years later, 4/40 of hyposmics developed PD, compared with 0/360 of normosmics,19 and at 5 years, those who had developed PD had lower mean scores on olfactory tests at baseline.20 Another small study of patients with idiopathic hyposmia found that 2/24 developed PD after 4 years of follow-up.21 The strongest evidence for the role of olfaction in PD prediction comes from the Honolulu-Asia Ageing Study.22 This pathological study examined olfaction using the Cross-Cultural Smell Identification Test in healthy Asian men, and prospectively correlated this with pathologically confirmed PD. In the first 4 years of follow-up, those in the lowest quartile of olfactory function had an OR of 5.2 for the development of PD, and those in the second lowest quartile had an OR of 3.1 for PD.

Despite this promise, some important caveats must be noted. Lead time (the interval between detection of olfactory abnormality and clinical disease) may be limited. In the Honolulu study, olfactory loss did not predict PD when assessed >4 years before disease onset.22 Similar findings were found in a smaller twin study of olfaction in PD.23 In the study of first-degree relatives, whereas 4/40 hyposmic patients developed PD in the first 2 years, only one other hyposmic patient had developed PD in the following 3 years.20 Specificity may be low—all in the lowest quartile of the Honolulu study had severe hyposmia, but only 10/549 (2%) developed PD.22 This low specificity suggests that olfactory testing will be insufficient by itself to indicate need for neuroprotective therapy. Finally, olfactory loss will probably also screen persons in preclinical stages of dementia, implying that olfactory testing would be a more effective screen for neuroprotective therapy that has a non-disease-specific action.
Autonomic dysfunction

In Stage 1 disease, there is prominent α-synuclein staining of unmyelinated projection neurons of the dorsal motor vagus, and recent studies suggest peripheral postganglionic sympathetic denervation may occur even earlier. Symptoms of autonomic dysfunction are experienced by 40–70% of PD patients, often at disease onset. There are now two prospective studies suggesting that constipation may predict PD. In the Honolulu study, a single question regarding bowel-movement frequency was asked at baseline. Those who reported a bowel-movement frequency of <1/day had a PD OR of 2.3 compared with those with 1 per day, and 4.8 compared with those with >2 per day. A second prospective record-linkage study demonstrated a 2.5-fold increased risk of PD in patients with a diagnosis of constipation. Interestingly, in both studies, this effect was evident 10–20 years before PD onset—if preclinical stages are shorter than 20 years, constipation may indicate an at-risk state as well as being an early disease manifestation. Other potential simple autonomic measures, such as orthostatic blood pressure, beat-to-beat variability and urinary symptoms, have not been studied as predictors, although abnormalities in beat-to-beat variability have been reported in idiopathic RBD.(see below).

One more expensive measure of autonomic function is cardiac metaiodobenzylguanidine (MIBG) scintigraphy, which measures postganglionic sympathetic cardiac innervation. The majority of patients with PD have abnormal MIBG scintigraphy, which appears to be present at the earliest stages of disease. MIBG scintigraphy is also abnormal in LBD and may help to distinguish LBD from AD. Recent studies have found abnormal scintigraphy in RBD, another preclinical marker of disease. Although there has been no direct confirmation of disease prediction, the high sensitivity of MIBG scintigraphy combined with pathological evidence of early sympathetic degeneration suggests considerable potential.

Again, caveats must be noted. First, the direct evidence that autonomic dysfunction predicts disease is less strong than it is for olfaction. Symptoms and signs of autonomic dysfunction are not universally present early in disease and frequently progress, which may indicate a lower sensitivity in detecting early stages. Specificity of autonomic symptoms is probably low—for example, constipation prevalence approaches 30%, compared with a PD prevalence of 1–2%. Markers which are potentially more specific, such as MIBG scintigraphy, are time-consuming and/or expensive.

STAGE 2 MARKERS

Depression

Depression is common in PD and is often found early in the disease course. Pathophysiology of depression in PD is complex and may involve dysfunction of numerous structures. Important brainstem nuclei linked to depression in PD include the dorsal motor nucleus of the vagus, serotonin neurons of dorsal raphae, substantia nigra and catecholaminergic neurons of locus ceruleus. Some of these structures are involved in Braak Stage 2. A retrospective cohort study based upon database diagnoses determined that those with a history of depression had a 2.4-fold increased risk of developing PD. A second national registry cohort found that those with a diagnosis of depression had a 2.4 to 3.2-fold increased risk of developing PD compared with patients with osteoarthritis and diabetes. The health professionals cohort study found that those with phobic anxiety were at a 1.5-fold increased risk of developing PD. Many case-control studies have also shown an increased PD risk in patients with history of depression. Finally, patients with depression may have abnormalities on SNpc transcranial ultrasound that are similar to PD (see below). Eventual use of depression as a disease predictor will likely be limited by low specificity—the large majority of persons with depression will never develop PD.

There have also been suggestions that early-life personality traits may be associated with PD. PD patients are often described as sober, reliable and conservative, and persons with PD have low scores on measures of novelty-seeking. Although these traits are considered lifelong, personality assessment may be biased by recall (recall of historical personality is affected by the present personality). If these personality changes emerge with time, they may be a marker of preclinical PD. Sensitivity and specificity of personality screens have also not been established.

REM sleep behaviour disorder

REM sleep behaviour disorder (RBD) is characterised by a loss of the normal atonia of REM sleep—affecting patients cry out, kick or thrash in association with dream content. RBD occurs in approximately a third of patients with PD, with an additional 20–50% demonstrating asymptomatic loss of REM atonia. RBD is common in MSA and LBD, and is seen occasionally in other parkinsonian neurodegenerative diseases. It has an unexplained striking male predominance. Prevalence has not been directly estimated, but estimations of sleep injury due to RBD range from 0.4% in persons over 70–0.5% of the general population. RBD has been predominantly linked with lesions in the brainstem, especially pontine areas such as the perlicus ceruleus and putative REM atonia nuclei analogous to the sublateraldorsal nucleus in mice. These pontine areas correspond most closely to Braak stage 2.

Several prospective studies have examined the risk of neurodegenerative disease in persons with idiopathic RBD (ie, RBD without evidence of neurodegeneration). The risk of developing a neurodegenerative disease in idiopathic RBD ranges from 19 to 58% at 5 years of follow-up, and from 40 to 68% after 10 years. Approximately half develop PD, and half develop dementia (most, if not all, of these are LBD). This high risk and long latency make RBD ideal markers for predicting PD. The high conversion rate to disease suggests the need for periodic follow-up examination, in order to detect treatable manifestations of disease early. In addition, the high conversion rate allows other potential predictors of PD to be studied; studies have demonstrated abnormalities in olfaction, colour vision, autonomic symptoms, MIBG scintigraphy and SNpc function in patients with RBD. Cognitive abnormalities are also found early in RBD, consistent with its potential as a predictor of dementia. It is unclear whether patients who are abnormal on these markers are at a higher risk of PD, but ongoing prospective studies should provide early answers in the next few years. A recent study has suggested that degree of sleep atonia loss, a polysomnographic marker of RBD severity, may predict a higher risk of Parkinson’s disease in patients with idiopathic RBD.

However, there are again caveats. First, not every PD patient has RBD; RBD may be associated with a specific PD subtype characterised by male sex, akinetic-rigid disease subtype, less medication response, more autonomic manifestations, EEG slowing and impaired cognitive function. If this indicates a different underlying pathophysiological process, findings in RBD patients may apply less well to those who develop PD without RBD. Second, in an age of neuroprotection, RBD will need to be screened for on a large scale. Two screening questionnaires for RBD have been designed. The first, a 10-item...
questionnaire, reported a sensitivity of 96% and specificity of 92% in normal controls.\textsuperscript{51} However, in patients with sleep complaints, specificity was only 56%, with misdiagnosis mainly due to behaviours such as talking in one’s sleep. A Japanese version of the same questionnaire found excellent sensitivity and specificity compared with controls (89% and 97%)\textsuperscript{51} and compared with patients with obstructive sleep apnoea (89% and 91%).\textsuperscript{52} A second 13-item questionnaire recently obtained a sensitivity of 82% with a specificity of 87%\textsuperscript{53} for RBD. A subset of seven of these questions directed specifically at dreaming-enactment behaviour showed similar sensitivity and specificity (88% and 81%)-this shortened questionnaire may be useful in large-scale cohort studies. Note that in a general population screening programme, a specificity even as good as 90% may be insufficient, as performing confirmatory polysomnogram in 10% of the population would be very labour-intensive and expensive. Finally, whether isolated REM sleep atonia without behavioural manifestations predicts PD is unknown-since these patients do not have symptoms, it is impossible to screen their RBD using questionnaires.\textsuperscript{54}

Despite these caveats, RBD has considerable potential as a marker. The high conversion rate to disease implies a marker with immediate clinical application; if a safe and effective neuroprotective agent were developed tomorrow, RBD patients may have to consider taking it. Also, patients with RBD may be the ideal candidates for clinical trials of neuroprotective agents, since their earlier stage of neurodegeneration provides an additional window of opportunity.

Other sleep disorders
Patients with PD have many other sleep manifestations, including insomnia and excessive daytime somnolence.\textsuperscript{25} These abnormalities are due to degeneration in diffuse structures, which include pontine structures that degenerate in Stage 2 disease.\textsuperscript{5} In the Honolulu-Asia ageing study, a single question assessing excessive daytime sleepiness was asked.\textsuperscript{54} Of those who reported sleepiness, the OR of PD was 2.8. However, only 235 of the 244 patients who reported sleepiness developed PD, so the utility of this question as a screen for PD is unclear. There have been no prospective studies assessing insomnia as a marker for PD.

STAGE 3 MARKERS
Dopaminergic PET and SPECT imaging
Dopaminergic innervation from the SNpc can be measured using radiolabelled ligands that label either pre- or postsynaptic dopaminergic terminals.\textsuperscript{55} Dopaminergic PET and SPECT have a very high sensitivity and specificity for parkinsonism (however, distinguishing PD from other causes of parkinsonism is limited).\textsuperscript{55} The reliability of dopaminergic imaging is such that most patients clinically diagnosed as having PD who have normal scans (ie, ‘SWEDD’\textsuperscript{s}) probably do not have PD.\textsuperscript{56} By extrapolating backwards from patients with early PD, studies have estimated that abnormalities may be measurable approximately 4–7 years before clinical symptoms.\textsuperscript{4, 57, 58} Heterozygotes for \textit{parkin} and PINK1 mutations may have abnormalities of Fluoro-dopa PET and raclocpride binding\textsuperscript{59} (although whether \textit{parkin} and PINK1 heterozygosity increase PD risk is unclear). Recent studies have documented loss of dopaminergic function on PET scanning in asymptomatic carriers of LRRK2 mutations, which in one case progressed with development of clinical PD.\textsuperscript{60} Patients with idiopathic RBD also can have abnormalities on dopaminergic imaging (although these are found only in a minority of cases).\textsuperscript{44} As mentioned above, hyposmic relatives of PD patients show decreased dopaminergic innervation.\textsuperscript{19} Dopaminergic innervation directly measures SNpc function, and therefore should identify patients whose progression does not follow the Braak model. However, despite compelling reasons to suggest predictive potential, no prospective studies have yet directly assessed predictive value of dopaminergic imaging in preclinical sporadic PD.

There are some important barriers to eventual application of PET and SPECT in an age of neuroprotection. First, procedures are expensive (and involve injection of ‘radioactive’ substances that some patients might refuse). This restricts their use to high-risk groups, or for use as a secondary screen. Consistent with their status as a stage 5 marker, there may be limited lead time (ie, 4–7 years). Diagnostic accuracy in premotor stages is also not established—although dopaminergic imaging is well established in clinically established PD, reliably defining subtle preclinical abnormalities may be less reliable.

Transcranial ultrasound
Transcranial ultrasound (TCS) imaging of the substantia nigra has promise as a non-invasive and inexpensive neuroimaging predictive marker. Approximately 80–90\% of PD patients have abnormal hyperechogenicity of the SN.\textsuperscript{51} Hyperechogenicity is found early in PD and may help in differential diagnosis of equivocal parkinsonian signs.\textsuperscript{61} TCS is normal in MSA and PSP. Of special interest, one study found that 60\% of clinically normal persons with hyperechogenicity had 18F-dopa uptake below normal,\textsuperscript{52} and hyperechogenicity has been correlated with mild motor slowing in elderly persons free of PD,\textsuperscript{53} suggesting that there are abnormalities in possible preclinical PD. Up to 40\% of patients with idiopathic RBD have abnormalities on TCS\textsuperscript{54} (this number, although clearly higher than controls, is not near 100\%, perhaps suggesting that not all idiopathic RBD patients are destined to develop PD). In addition, controls with abnormal TCS have olfactory dysfunction and depression.\textsuperscript{65}

There is some evidence that hyperechogenicity, rather than being a true marker of preclinical PD, may indicate a lifelong risk state for PD. First, abnormalities can be detected in 9\% of young healthy adults\textsuperscript{52} (however, note there is no direct evidence that young adults with abnormal TCS at increased risk—PD patients could develop TCS abnormalities de novo). Second, there is no correlation between the degree of hyperechogenicity and degree of dopaminergic innervation;\textsuperscript{66} nor does hyperechogenicity progress as disease progresses,\textsuperscript{67} which would be expected if TCS was a direct marker of neurodegeneration.

TCS has the advantages of non-invasiveness and relatively low cost. On the other hand, it is technician-dependent, and not all patients have adequate bone windows to allow imaging. So far, it has not been assessed outside research laboratories. Nonetheless, its high sensitivity in PD is promising.

Quantitative motor measures
At present, the diagnosis of parkinsonism is clinical and based upon subjective evaluation. This has led several investigators to try using quantitative motor measures to detect subtle motor changes. Potential quantitative motor measures include the alternate tap test, Purdue PegBoard, precision grip and lift task, alternate finger tap, and Timed up and Go.\textsuperscript{55} Most quantitative motor measures have not been studied for identification of preclinical disease. One study looked at wrist movements in patients with equivocal signs of parkinsonism, in a battery that included measurement of olfaction and mood.\textsuperscript{68} The battery
identified eventual PD diagnosis with 92% sensitivity and 68% specificity. However, as the battery was applied in persons who already had possible parkinsonism, it did not test a true preclinical state. Quantitative measures are also abnormal in idiopathic RBD, although less dramatically than non-motor markers.\(^{43} \) A potential limitation to quantitative motor testing is that subtle motor slowing occurs in up to 40% of elderly persons,\(^{49} \) suggesting suboptimal specificity. It is unclear whether these measures will perform better than clinical examination in distinguishing incidental mild parkinsonian signs from clinical disease. Finally, as with other stage 3 markers, it is unclear how much lead time would be gained.

Other potential predictors

Numerous visual changes occur in PD, many early in the course of the disease. Loss of colour vision is found early in PD and may be due to retinal degeneration.\(^{18} \) However, reliability of colour vision loss in early PD is unclear, especially since abnormalities progress with time.\(^{21} \) Contrast sensitivity loss is also found early in PD.\(^{70} \) No visual tests have been performed in persons before and after development of PD, but findings of abnormal colour vision in idiopathic RBD\(^{43} \) suggest that visual changes may have potential as a predictor.

Other studies in idiopathic RBD suggest additional potential predictors of PD. Patients with idiopathic RBD have increased \( \theta \) power and generalised slowing on EEG.\(^{72} \) This finding is similar to what is seen in dementia, suggesting that it is more likely to be a marker of preclinical dementia than PD. Patients with idiopathic RBD also have abnormalities on cognitive testing—these are similar to those seen in PD dementia/LBD, again consistent with a marker of preclinical dementia.\(^{73} \) Subtle fronto-executive changes are also often found in early PD, are often reversible with levodopa therapy and may have a different pathophysiological basis from that of PD dementia—these changes are relatively subtle, with overlap between patients and controls, suggesting insufficient sensitivity and specificity for detection of PD. Finally, there may be a PD-specific network of changes of whole-glucose utilisation on PET imaging.\(^{74} \) Similar changes were found in a group of idiopathic RBD patients, suggesting that these findings may be present in preclinical disease.\(^{75} \) Further follow-up of patients with RBD may be able to determine whether any of these factors can predict disease.

CONCLUSION

Although there is considerable promise for clinical predictors of PD, no single marker is presently able to predict the disease with good reliability and sensitivity. In planning for the eventual use of predictive markers, it may become necessary to design both simple non-invasive screens which can be applied to the general population, and more specific confirmatory tests for those who screen positive. Therefore, multiple lines of investigation should be encouraged. The instant that effective neuroprotective therapy becomes available, detection of early stages of disease will become critically important—therefore, the time to develop reliable predictive methods is now.

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