Pre-Motor Parkinson’s Disease: Concepts and Definitions

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Anthony Lang: Research project: Conception, organization, execution; Statistical analysis: N/A; Manuscript: Review and critique.

Full financial disclosures for the past year:
Andrew Siderowf

<table>
<thead>
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<th>Stock ownership in medically related fields</th>
<th>Intellectual property rights</th>
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Consultancies
- Teva Neuroscience; General Electric; Ipsen Pharmaceuticals

Advisory boards
- none

Partnerships: none

Honoraria: Teva Neuroscience; Oregon Health Sciences University

Grants: Avid Radiopharmaceuticals, NINDS, Michael J. Fox Foundation, National Parkinson Foundation

Anthony Lang

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Consultancies: Abbott, Allon Therapeutics, Astra Zenica, Avanir Pharmaceuticals, Biovail, Ceregene, Eisai, GSK, Medtronic, Merck Serono, Novartis, Santhera, Solvay, and Teva

Advisory boards: none

Partnerships: none

Honoraria: none

Grants: Institutes of Health Research, Dystonia Medical Research Foundation, Michael J. Fox Foundation, National Parkinson Foundation, and Ontario Problem Gambling Research Centre

Financial disclosure:
Andrew Siderowf is supported by a Morris K. Udall Parkinson’s Disease Research Center of Excellence grant from NINDS (NS-053488), and has been supported by SAP4100027296, a health research grant awarded by the Department of Health of the Commonwealth of Pennsylvania from the Tobacco Master Settlement Agreement under Act 2001-77. He has received consulting fees from Teva Neuroscience, Ipsen Pharmaceuticals, Schering-Plough and Merck Serono and General Electric. He has received speaking honorarium from Teva Neuroscience. He has received research support from Avid Radiopharmaceuticals.

Anthony Lang has served as an advisor for Abbott, Allon Therapeutics, Astra Zenica, Avanir Pharmaceuticals, Biovail, Boehringer-Ingelheim, Cephalon, Ceregene, Eisai, GSK, Lundbeck A/S, Medtronic, Merck Serono, Novartis, Santhera, Solvay, and Teva; received grants from Canadian Institutes of Health Research, Dystonia Medical Research Foundation, Michael J. Fox Foundation, National Parkinson Foundation, and Ontario Problem Gambling Research Centre; received publishing royalties from Saunders, Wiley-Blackwell, Johns Hopkins Press, and Cambridge University Press; and has served as an expert witness in cases related to the welding industry.
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Abstract

Parkinson’s disease (PD) has a prodromal phase during which non-motor clinical features as well as physiological abnormalities may be present. These pre-motor markers could be used to screen for PD before motor abnormalities are present. The technology to identify PD before it reaches symptomatic Braak Stage 3 (substantia nigra compacta (SNC) involvement) already exists. The current challenge is to define the appropriate scope of use of predictive testing for PD. Imaging technologies, like dopamine transporter imaging, currently offer the highest degree of accuracy for identifying pre-motor PD, but they are expensive as screening tools and abnormalities on these studies would only be evident at Braak Stage 3 or higher. Efficiency is greatly enhanced by combining imaging with a pre-screening test, such as olfactory testing. This two-step process has the potential to greatly reduce costs while retaining diagnostic accuracy. Alternatively, or in concert with this approach, evaluating high-risk populations (e.g. patients with rapid eye movement behavior disorder (RBD) or LRRK2 mutations) would enrich the sample for cases with underlying PD. Ultimately, the role of pre-clinical detection of PD will be determined by the ability of emerging therapies to influence clinical outcomes. As such, implementation of large-scale screening strategies awaits the arrival of clearly safe and effective therapies that address the underlying pathogenesis of PD. Future research will establish more definitive biomarkers capable of revealing the presence of disease in advance of SNC involvement with the promise of the potential for introducing disease modifying therapy even before the development of evidence for dopamine deficiency.

Keywords

Parkinson’s disease; early detection; sensitivity; specificity

Screening for disease before it begins or becomes symptomatic is emerging as the standard approach throughout medicine. It is widely accepted that risk factors for coronary heart disease and stroke can be identified and modified. Likewise, the question in screening for colon or breast cancer is not whether there should be screening, but how often. If screening and prevention is expected in these conditions, why should neurodegenerative disorders such as Parkinson’s disease (PD) be different? PD has a prolonged prodromal phase during which early signs of neuronal injury can be detected by technology that already exists. The missing elements in progress toward identifying PD during its “pre-motor” phase (the time before the classic motor features of tremor, rigidity and bradykinesia become apparent) are a better understanding of how to deploy existing diagnostic technology and, crucially, development of disease modifying treatments that are shown to be most effective when treatment is begun as early as possible. At present, there is an emerging consensus on the features that comprise pre-motor PD and growing body of evidence on the performance of several diagnostics as screening tools for PD.

Classification of pre-motor PD

Pre-motor PD can be divided into stages leading to manifest PD based on the presence of clinical, physiological or risk-markers of disease. Working backward from recognizable PD that could be diagnosed based on accepted criteria such as those by the UK Brain Bank\(^1\)
these stages include: 1) the pre-diagnostic phase, 2) the pre-motor phase, the 3) pre-clinical phase and 4) the pre-physiological phase. The term “Parkinson’s Disease at Risk Syndrome” (PARS)\(^2,3\) describes a hierarchical classification pyramid for patients who do not yet have clinical PD (figure 1).

**Pre-diagnostic phase**

At the second level, is the pre-diagnostic category, in which patients have classic PD symptoms and clinical features but do not fulfill PD diagnostic criteria at the next level; many patients have parkinsonian signs but do not technically fulfill criteria required for the diagnosis of PD.\(^4\) These patients with mild parkinsonian signs have the equivalent of mild cognitive impairment as a risk-state for Alzheimer’s disease (AD).\(^5\) Pre-diagnostic PD is conceptually distinct from the other levels of the PARS framework because clinical features of PD are apparent in the pre-diagnostic phase. As tests such as dopamine transporter (DAT) imaging become more widely used, patients with mild parkinsonian signs and biomarker evidence of dopamine deficiency may come to be diagnosed with PD, and this category would be reclassified as early, minimally symptomatic disease.

**Pre-motor phase**

Patients with pre-motor PD have non-motor symptoms such as decreased sense of smell, depression, and various gastrointestinal and other systemic features which have been shown to predate the classical motor features of Parkinson’s disease. Recognizable clinical features, including neuro-psychiatric and sleep symptoms, autonomic dysfunction, and olfactory loss often precede motor symptoms of PD (table 1). Although these features are not universal, they are present to variable degrees in most PD patients before the diagnosis of PD is made. Pre-motor features that have been strongly linked to PD include olfactory disturbance,\(^6\)\(^–\)\(^8\)\(^9\) excessive daytime sleepiness,\(^10\) RBD,\(^11\)\(^2,13\) constipation,\(^14\)\(^15\) and depression.\(^16\)\(^–\)\(^18\) The pre-motor phase may also have other features that have been linked less strongly to PD including subtle changes in cognition and personality or increases in fatigue or anxiety.\(^19\)\(^2,20\)\(^–\)\(^22\)\(^2,23\)\(^–\)\(^25\)

**Pre-clinical phase**

Preclinical PD refers to physiological changes that can be detected using biomarker techniques in the absence of any clinical features. Table 2 summarizes several of the tests that are available to identify pre-clinical PD. Changes on neuroimaging test such as DAT SPECT and [18F]-fluorodopa PET are examples of preclinical PD.\(^26\)\(^,\)\(^27\)\(^28\) Evidence of cardiac sympathetic denervation demonstrated by metaiodobenzylguanidine (MIBG)SPECT imaging of post-ganglionic sympathetic neurons is another example of a pre-clinical marker.\(^29\)\(^3,30\)\(^2,31\)\(^3,32\)\(^3\)\(^0\) Transcranial ultrasound of the midbrain is another modality that can reveal pre-clinical signs of PD. PD patients have an area of increased echogenicity in the substantia nigra.\(^33\)\(^–\)\(^3,35\) One study showed that more than 60% of “normal” subjects with increased echogenicity were also found to have a reduction of \(^18\)F-dopa uptake in the striatum.\(^36\) Another study showed that almost 50% of 1st degree relatives of PD patients show increased echogenicity of the substantia nigra.\(^37\) These modalities will be discussed in details in other sections of this supplement.

Biopsy of peripheral tissue such as autonomic plexi in the colon as representatives of the enteric nervous system could be markers of pre-clinical PD. Lewy pathology including Lewy bodies and Lewy neurites occurs in intrinsic, post-ganglionic neurons in the myenteric and submucosal plexuses from the esophagus to the colon.\(^38\)\(^–\)\(^40\) Correspondingly, Lewy pathology has been detected in tissue from the enteric nervous system of patients with incidental Lewy Bodies.\(^4\)\(^1\)\(^,42\) Two recent studies demonstrated Lewy pathology in colonic biopsy specimens in PD patients but not controls.\(^5\)\(^3\)\(^,\)\(^4,4\) From the perspective of the
progressive stages of PD proposed by Braak and his colleagues, involvement of the SNc as evaluated by pre-synaptic radioligands on PET or SPECT and presumably by nigral hyperechogenicity on transcranial sonography would establish the disease at Stage 3 or greater. Evidence of involvement of other regions such as the peripheral autonomic nervous system could occur in even earlier stages.

**Pre-physiological phase**

Finally, pre-physiologic patients have no evidence suggestive of PD but possess traits, such as a genetic mutation, which confer high risk of developing PD in the future. The term pre-physiological is intended to convey the idea that no signs of disease can be detected either clinically or by physiological probes such as dopamine imaging. Subtle molecular abnormalities could be present, but beyond detection by current technology. To an observer, an individual in the pre-physiological phase would appear normal by all measures, but might be known to possess an environmental or genetic risk factor. Genetic information about PD, in particular, is accumulating at an impressive pace, and testing for mutations in the parkin and LRRK2 genes are now commercially available. These gene tests have the potential to make the diagnosis of pre-clinical PD at the time of birth, since they identify a lifelong trait rather than an evolving pathological state. The risk imparted by genetic factors varies dependent on the particular gene involved. Individuals with certain environmental exposure could be considered in a pre-physiological state for the purpose of risk-stratification. Such epidemiological factors associated with PD include pesticide and other environmental exposures, demographic characteristics such as mid-life adiposity and lifestyle preferences like caffeine and tobacco use.

**Detection of Pre-motor PD: Methodological Issues**

The detection of pre-motor PD requires the integration of information on underlying disease frequency (incidence and prevalence) and results from diagnostic tests. In order to understand how to interpret information from such tests, it is useful to review a few basic concepts and terminology.

Many tests rely on the use of biomarkers to identify individuals with a given state or trait. The NIH Biomarkers Definitions Working Group defined a biomarker as “A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic response to a therapeutic intervention.” Frequently, biological tests are described as being state or trait biomarkers. A state biomarker measures the current status of disease. Trait biomarkers measure a characteristic that does not change over time, such as a genetic mutation. Examples of biomarkers used in screening for PD include imaging biomarkers such as dopamine imaging or biochemical biomarkers such as measuring alpha-synuclein levels in blood or spinal fluid.

Regardless of the technology or analyte, these biomarker tests can be evaluated using metrics common to all diagnostic tests: sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Values for sensitivity and specificity can be calculated for all diagnostic tests. These metrics are intrinsic characteristics of a test and, generally, do not vary depending on population being studied. Sensitivity is defined as the proportion of people with a given condition who have a positive test. Specificity is defined as the proportion of the people who do not have a given condition who have a negative test. Highly sensitive tests are clinically useful when the results are negative, implying that a person is very unlikely to have a disease. Conversely specific tests are useful when they are positive, indicating that disease is very likely to be present.
In contrast to sensitivity and specificity, the metrics or PPV and NPV are characteristics of a test applied in a specific population. PPV and NPV depend on the characteristics of the test (sensitivity and specificity) and on the underlying prevalence of the condition. PPV is defined as the proportion of people with a positive test that have disease. As the prevalence of PD increases in the population sampled, the PPV also increases. Therefore, when considering the utility of the features to be described as predictors of disease, it is important to consider both the frequency of the feature in the general population (false positives) as well as the expected frequency of Parkinson’s disease in that same population (prevalence). Negative predictive value is defined as the proportion of people who have a negative test who do not have disease. PPV and NPV are generally more relevant to making decisions for individual patients than sensitivity and specificity. PPV is the probability that a patient has a given condition after a test for that condition has come back positive. Figure 2 shows how sensitivity, specificity, PPV and NPV can be calculated from a 2 × 2 table.

One correlate of the foregoing discussion is that screening tests for PD need to be extremely sensitive if they are to be used in unselected populations. PD is relatively rare in the general population (~ 1 in 1000). As a result, the PPV of a test to detect PD will be low unless specificity is very high. This is because the PPV is defined as the number of positive tests/(the number of positive tests + the number of false positive tests). When a disease is rare, the number of people who could contribute false positive tests is much larger than the number who can be true positives. As a result, the specificity of the test, which can be represented as 1 - false positive rate, needs to be very high. Even if a test is 99% specific, in a disease like PD with an frequency of less than 1% of the population, the number of false positive tests will outnumber true positives. All diagnostic tests produce at least some false-positive and false-negative results. Even genetic tests can produce false positives results due to reduced penetrance. One solution to this problem is to screen only populations at highest risk. Figure 3 illustrates the advantages to this approach. Specific high-risk groups are described, below.

Another key issue is the cost of testing. Using current technology, it is possible to identify people that are at high risk for developing PD in the near future. For example, the DAT ligand Ioflupane(123I) ([I-123] N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane) (DATscan) for SPECT imaging is now available in the US. It has been commercially available in other parts of the world for a number of years. However, it is expensive and it is not yet clear whether payors and hospital formularies will adopt DATscan widely. In the case of screening for PD, large numbers of at risk individual would need to be scanned, and the vast majority would have normal testing. The challenge is to screen out low-risk cases using cheaper methods and to reserve DATscan only in highest risk individuals. Table 2 shows the accuracy, availability and cost of representative tests. Targeting high risk groups for screening and using a two-stage screening process that images only subjects who are at highest risk based on prescreening with a less expensive tests are two ways to address the problems described above; these approaches are obviously not mutually exclusive.

**Targeting of High Risk Groups**

Efficiency of screening for PD can be greatly enhanced by targeting individuals at highest risk for testing. The efficiency gained by targeting high-risk individuals is highlighted in table 3. The key concept is that raising the underlying prevalence of disease (i.e. enriching the sample for possible underlying PD) greatly increases the positive predictive value of a test. Several potential means could be used to increase the underlying prevalence of pre-motor PD in the target population. The two strongest risk factors for PD are having a family member that has a known genetic mutation and having a diagnosis of idiopathic rapid eye movement behavior disorder (RBD). Although penetrance of LRRK2 in incomplete, the risk of PD in a LRRK2 carrier is still approximately 20 times higher than in a non-carrier. The
risk of PD is greatest in patients with RBD. In fact, the 10-year risk of PD in a person with RBD is roughly equivalent to the lifetime risk in a LRRK2 carrier. However, certain barriers exist to using RBD as a marker of PD risk in large-scale studies including the fact that RBD appears to be a relatively rare disorder and a polysomnogram is required for diagnostic certainty. It may be possible to use surveys of patients or bed-partners to identify significant numbers of people with RBD symptoms. Surveys for RBD have been developed, and should be validated for use in large-scale screening studies.

Stratification based on common demographic factors may also raise the prior probability of PD to a modest degree. Life-style risk factors for PD including not smoking and drinking less caffeinated beverages have been extensively documented, and may produce up to a 5-fold modification of risk for PD. Other factors such as less mid-life adiposity, greater calcium consumption, fewer bowel movements in mid-life and environmental exposure to pesticides may also increase risk of PD.

Combining tests into a two-stage strategy

Two-stage screening where the first test is relatively inexpensive, but sensitive and moderately specific is an approach that reduces the number of expensive confirmatory tests. Using imaging as the second test in a two-step process reduces costs by lowering the number of scans (or other more definitive but expensive assessments) that need to be performed. To have a high overall accuracy rate, the first-stage test must be at least as sensitive as imaging. As a secondary screen, imaging can “weed-out” false positive tests, but it cannot re-capture false-negative cases that were not referred for imaging. The primary screen must also be reasonably specific, because the number of scans that needs to be performed depends on the false positive rate (1-specificity) of the primary screening test.

Olfactory testing is moderately sensitive for PD. Approximately 80% of newly diagnosed PD patients have abnormal olfaction, and moderately specific in that about 90% of low-risk individuals will have normal olfaction for their age. These findings suggest that olfactory testing is not sufficient by itself to screen for PD, but it may be a reasonable tool combined with a more sensitive test to detect pre-motor PD, especially in enriched populations already defined to have a higher proportion of PD cases than in the general population. The strategy of a two-step screen of olfactory testing followed by imaging has been tested in a study of first degree relatives of PD patients and is being tested in a large cohort of 5000 individuals in the Parkinson Disease At-Risk Syndrome (PARS) study (www.parsinfosource.com).

Timing and frequency of PD screening: Does Pre-motor PD have a predictable course?

The neuropathological staging system proposed by Braak and colleagues suggests a characteristic spread of Lewy Body pathology as the features of PD evolve. While there are clearly deviations from this pattern, predictable evolution of pathology does occur in many patients. It would be reasonable to propose that clinical features associated with different brain regions would also develop in an orderly fashion. If this were the case, understanding the order of onset of clinical and observable physiological features could guide screening strategies for pre-motor PD.

Several studies support the concept that dopaminergic deficits are present prior to the onset of clinical motor features of PD. One simple proof of this idea is that bilateral striatal dopaminergic deficits can be demonstrated in patients with unilateral clinical signs of PD. Studies that have attempted to back-project to the onset of a dopamine deficit in the striatum based on degree of dopamine loss in PD patients with varying disease duration have
generally suggested a range of between 2–8 years, although some estimates suggest a much longer latency period. Although several studies have suggested dependable evolution of clinical PD in patients with pathologically reduced striatal dopamine levels based on PET or SPECT, it is not certain that all individuals with pathologically reduced striatal dopamine will evolve into clinical PD.

As described above, olfactory deficits probably develop shortly before the onset of motor impairment in PD. Studies of the latency between olfactory and motor impairment are limited by the fact that most studies sample olfactory function once, and it is uncertain how long deficits have been present. Nonetheless, the available studies are relatively consistent and suggest a latency of 2–4 years. The duration of RBD prior to onset of a parkinsonian disorder is likely to be much longer. Again, as noted above, the latency may average approximately 10 years, but can be up to 20 years and cases with a latency period as long as 50 years have been reported. Finally, there may be gaps of 10–20 years between enteric symptoms such as constipation and mid-life obesity and onset of motor features of PD.

To implement screening for PD, it will be important to develop a more precise understanding of the time-line of emergence of non-motor clinical features of PD and the timing of the onset of dopaminergic abnormalities in the striatum. In almost any case, at-risk individuals would need to be screened on an ongoing basis to detect the earliest signs of disease. The frequency of screening depends on the time-course of the evolution of synuclein pathology. If pathology evolves rapidly then more frequent screening would be required to identify at risk individuals at a point when the pathological process could be interrupted. Conversely, indolent pathology would require less frequent screening intervals. A better knowledge of this time-line will inform the frequency with which screening would need to be performed. Clearly, screening as infrequently as possible without sacrificing accuracy provides the best return on investment. It is possible that the progression of PD pathology varies dependent on a number of pathogenetic factors that have yet to be determined. In the future, advances in our understanding may permit variable screening approaches depending on the presence of additional markers of predisposition to disease.

Potential Uses of Screening in Practice and Research

The means to detect PD before motor symptoms become apparent already exists. In some cases, PD can be detected before any physiological abnormalities are present. Several key issues must be addressed before pre-clinical testing can be recommended as part of clinical practice, and there are no recommendations from any official organization regarding screening for PD. In order to begin to formulate such recommendations, it is helpful to consider other disorders where predictive testing is available, such as Huntington’s Disease (HD). The International Huntington Disease Association (IHA) and World Federation of Neurology (WFN) produced guidelines for use of at-risk testing. These rules emphasize the right of the individual to decide whether or not to be tested, the need to provide information and counseling both before and after testing, the need for confidentiality and access of all at risk subjects to testing if they wish to be tested. Similar guidelines for implementation of predictive testing for PD could reduce the potential for breeches of confidentiality and ineffective communication of risk information.

Even if testing were available, there may be limited interest in being tested among at risk individuals. A test for parkin gene mutations is commercially available in the US, but there is little use of this test to identify at risk individuals outside of research settings. Likewise, dopamine transporter imaging has been available in Europe, and it has not been adopted in at-risk individuals. The experience with pre-clinical testing for HD illustrates some of the
issues related to uptake of pre-clinical diagnostic tests. Surveys of individuals at risk for HD conducted prior to the widespread availability of predictive testing suggested that 56–81% of family members were interested in testing. However, when testing became available, only 10–20% of at-risk individuals decided to be tested. In a survey of family members of PD patients, 76% of respondents expressed at least some interest in pre-symptomatic testing for PD. Not surprisingly, the interest increased substantially in a scenario where effective preventive treatment was available. These results show that individuals at risk for PD may not want to be tested for the sake of the knowledge alone, but would consider testing if “preventative” treatment was available.

While the role of predictive testing in the clinic remains uncertain, it is reasonable to pursue research studies to better understand the clinical and physiological features of pre-motor PD and to define the usefulness of various diagnostic tests in populations with different risk-profiles. A long term goal of this research will be to design clinical trials to test treatments that might prevent or delay the onset of motor features of PD. In order to design such a trial the conversion rate of individuals with specific risk factors needs to be defined, an operationalized definition of conversion to PD needs to be created and the sensitivity and specificity for risk of clinical PD for a given screening strategy needs to be calculated with reasonable precision. Each of these components is necessary for accurate sample size calculations in planning for a disease prevention trial. Providing data to address these issues forms the backbone of a rational research agenda in the area of pre-motor PD.

Reference List


Figure 1.
The PARS pyramid: In this conceptual model there are 4 stages that precede clinically manifest PD: pre-physiological, pre-clinical, pre-motor and pre-diagnostic. There are a relatively large number of individuals that have a pre-disposition to develop PD, but only a fraction progress to each succeeding level. Ultimately, the number of individuals who develop clinically manifest PD is a small fraction of the at-risk pool.
Figure 2.
Two-by-two table illustrating the four scenarios that could apply to diagnostic tests (true (A) and false (B) positives and true (D) and false (C) negative results). Sensitivity is calculated as A/A+C; Specificity is D/B+D. Positive predictive value (PPV) is calculated as A/A+ B and NPV is calculated as D/C+D. Because the denominator for PPV and NPV include values from both the affected (disease is present) and unaffected (disease is absent) groups, their value depends on the relative proportion of people from each group in a given population or study cohort. As the proportion of unaffected people increases, PPV also decreases and NPF increases.

<table>
<thead>
<tr>
<th>Test is positive</th>
<th>Disease is present</th>
<th>Disease is absent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Test is negative</td>
<td>C</td>
<td>D</td>
</tr>
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</table>
Figure 3.
Shows the effect of increasing prevalence on the ratio of false-positive to true-positive tests for less common disorders. Even very specific tests have high false-positive rates when a disease is not common. The figure shows that a test with 99% specificity still gives the same number of false positive tests as true positive tests in a disorder with population prevalence of 1/1000 (similar to PD). Assuming 95% sensitivity and 99% specificity, as prevalence increases, the proportion of positive tests that are true positives increases from about 50% to over 90%. (adapted from Tanner, Annals of Epidemiology 1996, 6:438–441).
**TABLE 1**

Possible premotor features of Parkinson’s disease

<table>
<thead>
<tr>
<th>Strongest evidence</th>
<th>Suggested links</th>
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<tr>
<td>Olfactory deficit</td>
<td>Other autonomic dysfunction (e.g., cardiac)</td>
</tr>
<tr>
<td>Constipation</td>
<td>Visual disturbances</td>
</tr>
<tr>
<td>Sleep disorders (EDS, RBD)</td>
<td>Cognitive changes</td>
</tr>
<tr>
<td>Depression and anxiety</td>
<td>Apathy</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Personality characteristics</td>
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</tbody>
</table>

EDS: excessive daytime sleepiness

RBD: rapid eye movement behavior disorder
### Table 2
Ancillary tests that can be used to diagnose pre-clinical PD

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Availability</th>
<th>Cost</th>
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<tr>
<td>Olfactory testing</td>
<td>++</td>
<td>+</td>
<td>Broad</td>
<td>Low</td>
</tr>
<tr>
<td>Neuropsychological testing</td>
<td>+</td>
<td>-</td>
<td>Broad</td>
<td>Moderate</td>
</tr>
<tr>
<td>Transcranial ultrasound</td>
<td>++</td>
<td>++</td>
<td>Restricted</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cardiac MIBG imaging</td>
<td>++</td>
<td>++</td>
<td>Broad</td>
<td>High</td>
</tr>
<tr>
<td>Dopamine transporter SPECT</td>
<td>++</td>
<td>++</td>
<td>Restricted</td>
<td>High</td>
</tr>
<tr>
<td>[18F]fluorodopa PET</td>
<td>++</td>
<td>++</td>
<td>Restricted</td>
<td>High</td>
</tr>
<tr>
<td>Genetic testing</td>
<td>++</td>
<td>++</td>
<td>Restricted</td>
<td>High</td>
</tr>
</tbody>
</table>

−= not clinically useful; + = somewhat useful; ++=sufficiently accurate to be useful
### Table 3

Identifying 100 at risk individuals: Impact of targeting high-risk groups for a two-stage screening approach using olfactory testing followed by dopamine transporter imaging. The table shows the number of individuals that would need to be screened based on 4 possible target populations to identify 100 subjects with abnormal imaging. The incidence rates are drawn from the literature for the general population, 1st degree relatives of PD patients, 1st degree relatives of known LRRK2 carriers and patients diagnosed with RBD. The primary screen (olfactory testing) is assumed to be 80% sensitive and 90% specific when applied within three years of disease onset.

<table>
<thead>
<tr>
<th>Population</th>
<th>PD incidence (cases/100,000 person-yrs)</th>
<th>Subjects to screen to identify 100 at risk</th>
<th>Number of PET/SPECT scans required</th>
<th>Percent of positive scans</th>
</tr>
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<tr>
<td>general population</td>
<td>40</td>
<td>104,156</td>
<td>10,503</td>
<td>1%</td>
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<tr>
<td>1st degree relatives of PD patients</td>
<td>120</td>
<td>34,719</td>
<td>3,559</td>
<td>3%</td>
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<tr>
<td>1st degree relatives of LRRK2 carriers</td>
<td>1,000</td>
<td>4,166</td>
<td>504</td>
<td>20%</td>
</tr>
<tr>
<td>Diagnosed with RBD</td>
<td>4,000</td>
<td>1,042</td>
<td>192</td>
<td>52%</td>
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